

IFW AF/1632
BEST AVAILABLE COPY

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Philip D. Ashton-Rickardt
Joseph T. Opferman

Serial No.: 09/993,363

Filed: November 14, 2001

For: INDUCTION OF IMMUNITY USING
INHIBITORS OF GRANZYMES

Group Art Unit: 1632

Examiner: Ram R. Shukla

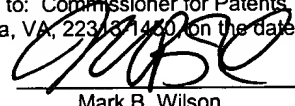
Atty. Dkt. No.: ARCD:382US

**CERTIFICATE OF MAILING
37 C.F.R. § 1.8**

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, VA, 22313-1450, on the date below:

August 9, 2004

Date


Mark B. Wilson

**RESPONSE TO NOTIFICATION OF NON-COMPLIANCE WITH 37 CFR 1.192(c)
MAILED JULY 9, 2004, AND SUBMISSION OF AMENDED APPEAL BRIEF**

M.S. APPEAL BREIF - PATENTS

Commissioner for Patents
Washington, D.C. 20231

Sir:

Appellants submit this Response to the Notication of Noncompliance with 37 CFR 1.192(c) mailed July 9, 2004, for which the one-month date for response is August 9, 2004.

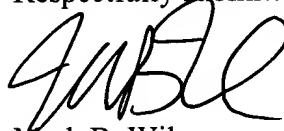
The fee for filing the Appeal Brief was paid in conjunction with the submission of the original Appeal Brief on April 26, 2004. Therefore, it is believed that no fees are due; however, should any fees be due, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworski Deposit Account 50-1212/ARCD:382US.

The Notification of Noncompliance states that the Appeal Brief filed on April 26, 2004, did not contain the items required under 37 CFR 1.192(c) or that the items were not under the proper heading or in the proper order. Appellants have rearranged the order of the headings in compliance with 37 CFR 1.192(c) and submit herewith an Amended Appeal Brief.

Appellants believe that this response and the Amended Appeal Brief submitted herewith is a complete response to the Notification of Missing Requirements mailed July 9, 2004.

Please date stamp and return the enclosed postcard to evidence receipt of this document.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Mark B. Wilson', written over the typed name.

Mark B. Wilson
Reg. No. 37,259
Attorney for Appellants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
512/474-5201

Date: August 9, 2004



CERTIFICATE OF MAILING
37 C.F.R. §1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: M.S. Appeal Brief Patents, U. S. Patent and Trademark Office, P. O. Box 1450, Alexandria, VA 22316-1450, on the date below:

August 9, 2004
Date

Mark B. Wilson

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Philip D. Ashton-Rickardt
Joseph T. Opferman

Serial No.: 09/993,363

Filed: November 14, 2001

For: INDUCTION OF IMMUNITY USING
INHIBITORS OF GRANZYMES

Group Art Unit: 1632

Examiner: Ram R. Shukla

Atty. Dkt. No.: ARCD:382US

AMENDED APPEAL BRIEF

TABLE OF CONTENTS

	Page
I. REAL PARTY IN INTEREST	2
II. RELATED APPEALS AND INTERFERENCES.....	2
III. STATUS OF THE CLAIMS	2
IV. STATUS OF THE AMENDMENTS	3
V. SUMMARY OF THE INVENTION	3
VI. ISSUES ON APPEAL	4
VII. GROUPING OF THE CLAIMS.....	4
VIII. ARGUMENT	6
A. SUMMARY OF THE ARGUMENT	6
1. The Written Description Rejection Should be Overturned.....	6
2. The Enablement Rejection Should be Overcome	6
B. STANDARD OF EVIDENCE.....	8
C. THE WRITTEN DESCRIPTION REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ARE OVERCOME	8
1. Nature of the Rejection	8
2. There is Sufficient Written Description Support in the Specification for the Term “Serp or Serpin Mimetic”	10
3. The Subject Matters of Claims 34, 35, 64, and 65 are Separately Patentable with Regard to the Written Description Rejection.	13
4. The Subject Matters of Claims 35 and 65 are Separately Patentable from those of Claims 34 and 65 with Regard to the Written Description Rejection.	15
5. The Subject Matters of Claims 37 and 67 are Separately Patentable from those of the Remaining Claims with Regard to the Written Description Rejection.	15
D. THE ENABLEMENT REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ARE OVERCOME	16
1. Nature of the Rejection	16
2. The Claims as Written are Sufficiently Described in the Specification to Meet the Enablement Requirement.	17
3. LCMV Infection in the Mouse is a Well-known and Established Model for Viral Infection in Humans, Including HIV Infection.	20
4. The Art of Gene Therapy and Cell Therapy are not so Unpredictable as to Preclude Enablement.	23
5. The Subject Matters of Claims 42-44 and 71-73 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.	25

TABLE OF CONTENTS
(continued)

	Page
6. The Subject Matters of Claims 43 and 72 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.....	25
7. The Subject Matters of Claims 44 and 73 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.....	26
IX. CONCLUSION.....	26

APPENDICES:

APPENDIX A – Pending Claims

APPENDIX B – Cited Cases & Statutes

APPENDIX C – Declaration of Raymond Welsh, Ph.D.



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Philip G. Ashton-Rickardt and
Joseph T. Opferman

Serial No.: 09/993,363

Filed: November 14, 2001

For: INDUCTION OF IMMUNITY USING
INHIBITORS OF GRANZYMES

Group Art Unit: 1632

Examiner: Ram R. Shukla

Atty. Dkt. No.: ARCD:382US

AMENDED APPEAL BRIEF

M.S. APPEAL BRIEF - PATENTS

Commissioner for Patents

P. O. Box 1450

Alexandria, VA 22313-1450

Dear Sir:

Appellants hereby submit an original and two copies of this Amended Appeal Brief to the Board of Patent Appeals and Interferences in response to the Notification of Non-Compliance with 37 C.F.R. 1.192(c) mailed July 9, 2004, the response to which is due August 9, 2004. The appropriate fee for filing the Appeal Brief was included with the original Appeal Brief received by the Office on April 26, 2004. It is believed that no other fees under 37 C.F.R. §§ 1.16 to 1.21 are occasioned by the filing of this paper; however, should the Commissioner determine otherwise, the Commissioner is hereby authorized to deduct said fees from Fulbright & Jaworski Deposit Account No. 50-1212/ARCD:382US.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee of record of this application, The University of Chicago, Chicago, IL.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 26-35, 37-40, 42-44, 48-50, and 61-74 were pending and under consideration at the time of the final Office Action dated October 20, 2003.

In response to a Restriction Requirement filed on December 12, 2004, Appellants elected, without traverse, to prosecute claims 1-25, *i.e.*, the Group I claims. However, following a discussion with the Examiner, Appellants changed their election to the Group II set of claims in a Substitute Response to the Restriction Requirement submitted on January 14, 2003.

The Group II invention encompasses therapeutic methods for enhancing or inducing immunity comprising administering to a subject in need thereof compositions comprising expression constructs encoding granzyme inhibitors, as set forth in claims 26-50. In response to a Species Election Requirement seeking election of both a species of disease treated and a species of inhibitor, Appellants elected HIV as the species of disease treated and PI9 as the species of inhibitor for initial examination in the Substitute Response to the Restriction Requirement and Species Election Requirement submitted on January 14, 2003. In view of this, claims 1-25 and 51-60 were withdrawn from further consideration pursuant to 37 C.F.R. §1.142(b) as being drawn to a non-elected invention in the Office Action dated March 19, 2003, and were subsequently canceled by the Appellants in the Amendment and Response to the Office Action submitted on June 17, 2003. The Amendment and Response to the Office Action

submitted on June 17, 2003, also included cancellation of claims 36, 41, and 45-47, as well as the addition of new claims 61-74. As a result, claims 26-35, 37-40, 42-44, 48-50, and 61-74 were pending at the time of the final Office Action dated October 20, 2003.

The final Office Action dated October 20, 2003, rejected all of the pending claims. Thus, claims 26-35, 37-40, 42-44, 48-50, and 61-74 are pending in the application and are the subject of this Appeal Brief. A copy of the claims as they are on appeal is contained in Appendix A.

IV. STATUS OF THE AMENDMENTS

There are no outstanding amendments in regard to this application

V. SUMMARY OF THE INVENTION

As described in the Summary of the Invention section, at pages 5-11 of the specification, and the pending claims as attached below in Appendix A, the presently claimed invention provides granzyme B inhibitors, such as the endogenous serpins among others, for enhancement and/or inducement of immunity. Thus, the invention provides methods of protection against clonal exhaustion and generation of sufficient numbers of CTL-memory cells which can provide long-term immunity. For example, this immunity can result in protection against viral infections.

In presently claimed embodiments, the invention related to methods for enhancing immunity to a viral infection comprising administering to a patient a composition comprising a granzyme inhibitor. In some embodiments, the granzyme inhibitor inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme. In other embodiments, the granzyme inhibitor inhibits granzyme function. The granzyme inhibitor can be a polypeptide, an anti-granzyme antibody, or a small molecule. In some specific embodiments, the polypeptide is a serpin. Serpins are endogenous serine protease inhibitors and some examples of serpin useful in the context of the present

invention are SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, and plasminogen activator inhibitor 2 (PAI-2). In some particular embodiments, the polypeptide is a mimetic that comprises a sequence that binds to granzyme and has granzyme inhibitory function. The methods of the present invention provide enhanced immunity to a wide variety of viruses. Although not limited to any particular viral types or strains some examples of viruses to which immunity may be enhanced include HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomegalovirus, Herpes simplex 1 and 2, hepatitis G, enterovirus, dengue fever virus, rabies virus.

The invention also provides methods for enhancing immunity comprising: obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a granzyme inhibitor under the control of a promoter active in the cytotoxic T-lymphocyte; and administering the cytotoxic T-lymphocyte to a subject in need thereof.

VI. ISSUES ON APPEAL

The issues on appeal are as follows:

A. Are claims 26-35, 37, 42-44, 48-50, 61-65, 67, and 71-73 unpatentable for failure to meet the written description requirement of 35 U.S.C. §112, first paragraph?

B. Are claims 26-35, 37-40, 42-44, 48-50, and 61-74 unpatentable for failure to meet the enablement requirement of 35 U.S.C. §112, first paragraph?

VII. GROUPING OF THE CLAIMS

The claims stand or fall with respect to each of the issues on appeal as set forth below. Arguments supporting that these claims stand or fall separately are set forth in the Argument section of this Brief.

Regarding the written description rejection, claims 38-40, 66, 68-70, and 74 are not rejected on this basis. Therefore these claims stand or fall separately from the remaining claims in this regard. Additionally, this rejection is based upon whether the instant specification supports the full scope of the claim term “serpin or serpin mimetic.” Appellants vigorously dispute that the scope of this term is not supported by the specification. However, claims 34, 35 and 64 contain additional function definition of the activity of the serpin or serpin mimetic that is employed in independent claims 30 and 26 respectively. Therefore, claims 34, 35, 64, and 65 stand or fall separately from the remainder of the claims in regard to the rejection. Further, claims 35 and 65 contain a more specific functional definition regarding the serpin or serpin mimetic than do claims 34 and 64 respectively, and, therefore, should stand or fall separately from claim 34. Additionally, claims 37 and 67 specifically recite that the serpin or serpin mimetic of claims 30 and 26 respectively is a serpin and stand or fall separately from the remainder of the claims in this regard.

Regarding the enablement rejection, the Action holds that the specification does not adequately enable the scope of the claims regarding the virus or viral infection to be combated by the practice of the claimed methods. Appellants, of course, vigorously dispute this rejection. However, Appellants point out that claims 42-44 and 71-73 contain more specific definitions of the virus to be combated. Therefore, these claims should stand or fall separately from the remaining claims in regard to the enablement rejection. Additionally, claims 43 and 72 are directed towards embodiments where the virus is specifically HIV and should stand or fall separately from all the remaining claims in regard to the enablement rejection. Likewise, claims 44 and 73 are directed specifically to LCMV and stand or fall separately from all the remaining claims based on this fact.

VIII. ARGUMENT

A. Summary of the Argument

1. *The Written Description Rejection Should be Overturned*

Claims 26-35, 37, 42-44, 48-50, 61-65, 67, and 71-73 are rejected under 35 U.S.C. §112, first paragraph, as lacking written description support in the Specification. According to the Office Action dated October 20, 2003, there is insufficient written description support for the term “serpin or serpin mimetic” in the Specification. In particular, the Action indicates that the Specification fails to describe a “representative numbers of species of the serpin or serpin mimetics that would enhance or induce immunity to any viral infection and that would inhibit granzyme function or activity by any mechanisms.” Office Action dated October 20, 2003, page 3, paragraph 2. The Action indicates that “specific characteristics or identifying characteristics of the serpins or serpin mimetics encompassed by the invention” must be disclosed for there to be written description support. Office Action dated October 20, 2003, page 3, paragraph 2.

Appellants traverse, and in their response have cited a substantial amount of information from the Specification pertaining to serpins and serpin mimetics, including specific and identifying characteristics of the serpins and serpin mimetics encompassed by the claimed invention. The information pertaining to serpins and serpin mimetics included in the Specification is sufficient to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed.

2. *The Enablement Rejection Is Overcome*

Claims 26-35, 37-40, 42-44, 48-50, and 61-74 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly

connected, to make and/or use the invention for reasons of record set forth in the Office Action dated March 19, 2003. According to the Action dated March 19, 2003, the Examiner's concerns appear to be focused on three main areas: (1) the scope of the claims; (2) the alleged unpredictability of the art of gene therapy and CTL therapy; and (3) a concern for lack of applicability of the results disclosed in the specification to HIV disease. Appellants traverse each of these rejections. The Action dated October 20, 2003, indicates that the declaration of Dr. Raymond Welsh, submitted in response to the Office Action dated March 19, 2003, is persuasive to establish that LCMV infection is a model for HIV infection in humans. However, the declaration is said to not be found sufficient to address specific information as to how to enhance or induce immunity in a HIV infected subject.

Based on the disclosure in the Specification, particularly those sections pertaining to treatment of viral disease, serpins, and serpin mimetics, Appellants argue that one of ordinary skill in the art would be able to make and/or use the claimed invention without undue experimentation.

Regarding the issue of unpredictability of gene therapy and cell therapy, Appellants note that even though gene therapy and cell therapy using CTLs may not be commonplace today from a clinical standpoint, they most certainly are sufficiently enabling for patenting. While each case is taken on its own merits, the PTO cannot cling to the notion that gene therapy or CTL therapy is *per se* lacking in enablement. It is critical to make the distinction between the necessary showing under 35 U.S.C. §112, and that needed to establish clinical efficacy. Controlling precedent makes it clear that even those therapies ultimately without use in the clinic are of value, and therefore may be patented.

Further, Appellants note that one of ordinary skill in the art would readily recognize that the LCMV mouse is a well-known and well-established model for HIV infection in humans, and that in view of the disclosure in the Specification, one of ordinary skill in the art would be able to make and/or use the invention without undue experimentation. In support of this position, Appellants have provided the declaration of Raymond M. Welsh, Ph.D., Professor in the Department of Pathology at the University of Massachusetts Medical Center.

B. Standard of Evidence

As an initial matter, Appellants note that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994. *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by “substantial evidence” within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that “the ‘substantial evidence’ standard asks whether a reasonable fact finder could have arrived at the agency’s decision.” *Id.* At 1312. Accordingly, it necessarily follows that an Examiner’s position on Appeal must be supported by “substantial evidence” within the record in order to be upheld by the Board of Patent Appeals and Interferences.

C. The Written Description Rejections Under 35 U.S.C. §112, First Paragraph, are Overcome

1. Nature of the Rejection

Claims 26-35, 37, 42-44, 48-50, 61-65, 67, and 71-73 are rejected under 35 U.S.C. §112, first paragraph, as containing that which was not described in the Specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The reasons for the rejection are

set forth in the Office Action dated March 19, 2003, and the Office Action dated October 20, 2003.

According to the Office Action dated March 19, 2003, the Specification “does not provide sufficient written description support for the claimed genus of granzyme inhibitors.” Office Action dated March 19, 2003, page 3, paragraph 1. The Action also indicates that the Specification does not provide sufficient teaching regarding the subgenus of modulators and inhibitors of granzyme activity, including inhibitors of granzyme transcription and translation. In this regard, the Action indicates that the Specification fails to describe the “complete structure” or “other relevant identifying characteristics (*i.e.*, other than nucleotide sequence)” of a representative number of species of the genus and subgenus of granzyme inhibitors. Office Action dated March 19, 2003, page 3, paragraph 1.

Appellants, in their response to the Office Action dated March 19, 2003 and in view of their Amendment to the claims, argued for written description support for the term “serpin or serpin mimetic.” The Office Action dated October 20, 2003, however, stated that there is insufficient written description support for the term “serpin or serpin mimetic” in the Specification. In particular, the Action indicates that the Specification fails to describe a “representative numbers of species of the serpin or serpin mimetics that would enhance or induce immunity to any viral infection and that would inhibit granzyme function or activity by any mechanisms.” Office Action dated October 20, 2003, page 3, paragraph 2. The Action indicates that “specific characteristics or identifying characteristics of the serpins or serpin mimetics encompassed by the invention” must be disclosed for there to be written description support. Office Action dated October 20, 2003, page 3, paragraph 2. Therefore, there is said to be

insufficient written description support for the claimed invention. Appellants traverse this rejection.

2. *There is Sufficient Written Description Support in the Specification for the Term “Serpín or Serpín Mimetic”*

Present independent claims 26 and 30 recite “serpín or serpín mimetic.” The Specification provides sufficient written description support for the term “serpín or serpín mimetic.” The written description support in the Specification includes specific and/or identifying characteristics of the claimed serpins or serpin mimetics encompassed by the claimed invention.

The Specification clearly discloses a representative number of species of the genus “serpín and serpín mimetics.” See Specification, page 4, lines 20-26; page 5, lines 21-23; page 15, lines 15-16; Page 15, line 21 through page 16, line 4; Page 19, lines 12-14; Page 37, lines 22-24. In particular, a review article pertaining to serpins is cited on page 4, line 21 of the Specification. Examples of particular serpins useful in the context of the invention are cited in the Specification, and include SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, and plasminogen activator inhibitor (PAI-2). Specification, page 6, lines 21-24. Further, one of skill in the art would be familiar with the substantial amount of information that is available pertaining to serpins and the numerous types of serpins that have been identified, as well as with the nucleotide sequences of genes encoding these serpins and serpin mimetics.

A detailed description of serpin mimetics useful in the claimed invention is provided in the Specification. Specification, page 6, line 26 to page 7, line 23. In addition, each of the Examples delineated in the Specification provides substantial information pertaining to serpins, in particular SPI6 and PI9, in the context of the present invention. Specification, Examples 1-13 (page 67, line 22 through page 89, line 4). Therefore, Applicants assert that the Examiner’s

concerns regarding lack of a representative number of species of serpins or serpin mimetics have been overcome.

Further, the Examiner's concerns regarding lack of identifying characteristics of the serpins or serpin mimetics have been overcome. As discussed above, the Specification provides substantial information pertaining to serpins and serpin mimetics, and one of ordinary skill in the art would be familiar with the substantial information that is known about various types of serpins. For example, the Specification provides substantial information pertaining to PI9 and PI9 mimetics. See Specification, page 4, lines 23-26; page 6, lines 21-24; page 6, line 26 through page 7, line 23; page 15, lines 16-17; page 19, lines 12-14; page 27, lines 22-24; and Example 13 (page 88, line 30 through page 89, line 4). Substantial information pertaining to PI9 mimetics is provided in the Specification. Specification, page 6 line 26 through page 7, line 23. In addition, Example 13 provides information pertaining to the use of PI9 as an agent to increase the potency of human cytolytic lymphocytes. Specification, page 88 line 30 through page 89, line 4.

The objective standard for determining compliance with the written description requirement is whether "the description clearly allow[s] persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 U.S.P.Q.2d 1614, 1618 (Fed. Cir. 1989). The Federal Circuit has also noted that possession of the claimed invention can be shown by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997).

The Specification of the instant application allows one of skill in the art to recognize that Appellants invented what is claimed. In particular, the Specification provides substantial information pertaining to serpins and serpin mimetics, and the identifying characteristics of the serpins or serpin mimetics that are encompassed by the claimed invention. That the claimed invention encompasses all members of the genus of serpins or serpin mimetics should not be dispositive, as long as one of skill in the art can recognize that the inventor invented what is claimed.

The Specification teaches a large number of representative members of the genus of serpins, and provides substantial specific or identifying characteristics pertaining to members of the genus of serpins such as PI9 and subgenuses such as mimetics of PI9. One of ordinary skill in the art would also be familiar with the vast amount of information known in the art pertaining to serpins and serpin mimetics. Additionally, in view of the information provided in the Specification pertaining to mimetics, one of skill in the art would be able to understand how to make and use the claimed invention with regard to serpin mimetics and mimetics of PI9. This is particularly true in view of the substantial information provided by the Examples in the Specification discussed *supra*.

The Examiner, in his response, appears to be arguing that Appellants must prove that each and every serpin or serpin mimetic encompassed by the claimed invention must be shown to enhance or induce immunity to a viral infection and inhibit granzyme function or activity by any mechanism. See Office Action dated October 20, 2003, page 3, paragraph 2 (“The sections of the specification referred to by the applicants in their response do not describe representative number of species of serpin or serpin mimetics that would enhance or induce immunity to any viral infection and that would inhibit granzyme function or activity by any mechanisms.”). Such

an interpretation of the laws of written description is erroneous. All that is required to meet the written description requirement is that the Specification “describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.” See, e.g., *Vas-Cath, Inc., v., Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991). Appellants assert that the detailed description of serpins and serpin mimetics set forth in the Specification is sufficient to satisfy the written description requirement. In addition, “[t]here is a strong presumption that an adequate written description of the claimed invention is present when the application is filed.” *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Furthermore, the PTO has the initial burden of presenting evidence or reasons by persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims. *Id.* Appellants assert that the Examiner, by arguing that Appellants must prove that each and every serpin or serpin mimetic encompassed by the claimed invention must be shown to enhance or induce immunity to a viral infection and inhibit granzyme function or activity by any mechanism, has failed to meet this initial burden.

For all of these reasons, the written description rejection to all of the claims under 35 U.S.C. §112, first paragraph, should be reversed by the Board. Further, for reasons set forth below, there are additional reasons why the subject matters of various dependent claims are allowable over this rejection.

3. *The Subject Matters of Claims 34, 35, 64, and 65 are Separately Patentable with Regard to the Written Description Rejection.*

Claims 34, 35, 64, and 65 contain additional function definition of the activity of the “serpin or serpin mimetic” that is employed in independent claims 30 and 26 respectively.

Specifically, claims 34 and 64 set forth that “the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.” Claims 35 and 65 set forth that, “the serpin or serpin mimetic inhibits granzyme function.”

In view of these distinctions of claims 34, 35, 64, and 65 from the remaining claims on appeal vis-à-vis the definition of “serpin or serpin mimetic,” The subject matters of these claims are separately patentable over the remaining claims. While Appellants believe that the full scope of all claims on appeal are supported by adequate written description, it is possible that the Board could conclude that, claims with more specific functional definitions of the activity of the claimed serpin and serpin mimetics meet the requirements of 35 U.S.C. §112, second paragraph, while the remaining claims do not. In this regard, Appellants would point out that the statements of the Action at page 3, that the specification does “not disclose any specific characteristics or identifying characteristics of the serpins or serpin mimetics encompassed by the claimed invention,” are particularly unsupported in regard to claims containing functional definitions. In fact, the Examiner has provided no evidence of record to support that the full scope of claims 34, 35, 64, and 65 is not supported by the specification.

Therefore, the subject matters of claims 34, 35, 64, and 65 are allowable over the written description rejection and stand or fall separately from those of the remainder of the claims in regard to the rejection.

4. *The Subject Matters of Claims 35 and 65 are Separately Patentable from those of Claims 34 and 65 with Regard to the Written Description Rejection.*

As set forth above, claims 35 and 65 contain an even more specific functional definition regarding the serpin or serpin mimetic than do claims 34 and 64 respectively, setting forth that set forth that, “the serpin or serpin mimetic inhibits granzyme function.”

The Action contains no support for its position that claims 35 and 65, lack adequate written description in the specification. Further, it is clear from the specification that a serpin or serpin mimetic that inhibits granzyme function, will work in the context of the invention and that Appellants had possession of this aspect of the invention at the time of filing of the application.

Therefore, the subject matters of claims 34, 35, 64, and 65 are allowable over the written description rejection and stand or fall separately from those of the remainder of the claims in regard to the rejection.

5. *The Subject Matters of Claims 37 and 67 are Separately Patentable from those of the Remaining Claims with Regard to the Written Description Rejection.*

Claims 37 and 67 specifically recite that the serpin or serpin mimetic of claims 30 and 26 respectively is specifically “a serpin.” As such these claims are of differing scope from the remaining claims, are separately patentable, and stand or fall separately from the remainder of the claims.

The Action does not present specific evidence as to why the use of serpins in the context of the invention is not supported in the specification. Further, the fact that claims 38 and 68 have not been rejected on the basis of lack of written description, suggests that at least eight specific serpins that are useful in the context of the invention have adequate written description. In this

case, there should certainly be adequate support for a generic claim to serpins, as set forth in claims.

In view of the above, the Board could find that the subject matter of claims 37 and 67 is patentable, even if the subject matter of the other claims is not. Therefore, these claims stand or fall separately from the remaining claims in regard to the written description rejections.

D. The Enablement Rejections Under 35 U.S.C. §112, First Paragraph, are Overcome

1. Nature of the Rejection

Claims 26-35, 37-40, 42-44, 48-50, and 61-74 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the Specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record set forth in the Office Action dated March 19, 2003.

According to the Action dated March 19, 2003, the Examiner's concerns appear to be focused on three main areas: (1) the scope of the claims; (2) the alleged unpredictability of the art of gene therapy and CTL therapy; and (3) a concern for lack of applicability of the results disclosed in the specification to HIV disease. Appellants traverse each of these rejections.

The Action dated October 20, 2003, indicates that the declaration of Dr. Raymond Welsh, submitted in response to the Office Action dated March 19, 2003, is persuasive to establish that LCMV infection is a model for HIV infection in humans. However, the declaration is said to not be found sufficient to address specific information as to how to enhance or induce immunity in a HIV infected subject. While the Action admits that the declaration is sufficient to establish that LCMV infection is a model for HIV infection in humans, it argues that the working examples do

not support enablement for HIV infection since the working examples disclose LCMV infection in a transgenic mouse that expresses SP16. The Action argues that the LCMV mouse is not recognized as an art-recognized model for HIV infections in human subjects. It is said that a transgenic mouse cannot be compared to a virus-infected human subject since all cells of a transgenic mouse have integrated a candidate gene, whereas in a subject a vector has to be administered. Further, an HIV infected subject already has a virus infecting its cells and the serpin will be provided later on, whereas in the transgenic mouse model SP16 is expressed and then LCMV infection is carried out.

Regarding the issue of unpredictability, the Action argues that the claimed invention is “not enabled by the instant Specification because the art of gene therapy and of cell therapy using CTLs is unpredictable as recognized in the art.” Office Action dated March 19, 2003, page 5, paragraph 2. Although the PTO has issued patents pertaining to gene therapy, these patents were “issued for specific conditions with specific vectors and as such could not be generally used in treating any condition.” Office Action dated October 20, 2003, page 5, paragraph 2.

Appellants traverse this rejection.

2. *The Claims as Written are Sufficiently Described in the Specification to Meet the Enablement Requirement.*

The Examiner first addresses concerns regarding the breadth of the claims. More particularly, the Examiner notes that the claimed invention is drawn to a method of inducing immunity or enhancing immunity in a subject with any disease with any granzyme inhibitor. As a result, the Examiner asserts that practicing the invention would require undue experimentation.

The presently pending claims encompass methods for enhancing or inducing immunity to a viral infection that involves expressing a serpin or a serpin mimetic. As discussed and cited

above, the Specification provides a substantial amount of information pertaining to serpins and serpin mimetics, as well as specific PI9 and PI9 mimetics.

The Specification also provides a substantial amount of information pertaining to enhancing or inducing immunity to a viral infection. A discussion pertaining to the epidemiology of viral infection is provided on page 2, lines 17-23 of the Specification. The role of CTLs in viral infection is discussed in the Specification on page 3, line 1 through page 5, line 17; page 13, line 20 through page 14, line 24; and page 14, line 27 through page 16, line 4. Application of the invention to the treatment of viral disease is discussed in the Specification on page 8, lines 11-15. The inventors discuss that they have demonstrated the ability to use granzyme B inhibitors to successfully eliminate virus, as shown using the transgenic mouse model of LCMV infection. Specification, page 14, lines 6-17. Application of the methods disclosed in the Specification to treatment of HIV disease is discussed on page 10, lines 6-19. Animal models of viral infection, including a discussion of techniques such as CTL assays, are discussed in the Specification on page 50, line 10 through page 52, line 12 of the Specification. Human treatment protocols of viral infection are addressed in the Specification on page 63, line 28 through page 67, line 7.

According to the Examiner, "all of the sections of the specification s referred to by the applicants are general statements and do not provide any specific information as to how immunity to any viral infection, in particular HIV will be enhanced or induced." Office Action dated October 20, 2003, page 4, paragraph 3. Appellants disagree. As set forth in detail below, the declaration of Dr. Raymond Welsh establishes that one of ordinary skill in the art, upon reading the Specification, including the specific sections cited above, would be able to make and use the claimed invention without undue experimentation.

Further, the working examples address application of the invention to treatment of viral disease. In particular, the working examples demonstrate the effect of SPI6 on the LCMV-infected mouse. Example 1 provides general information pertaining to LCMV infection in mice and CTL assays. Specification, page 67, line 22 through page 69, line 19. Example 2 demonstrates that mouse Serpin SPI6 protects cells from apoptosis by granzyme B. Specification, page 69, line 24 through page 71, line 21. Example 7 discusses results pertaining to the clonal exhaustion induced by LCMV infection in mice. Specification, page 78, line 15 through page 79, line 2. Example 12 demonstrates the protective effect of SPI6 on CTLs in LCMV infection, and demonstrates that granzyme B is involved in the development of memory cells. Specification, page 84, line 10 through page 88, line 25.

The working Examples set forth above pertain disclose LCMV infection in a transgenic mouse that expresses SP16. According to the Examiner, “[a] transgenic mouse cannot be compared to a subject since all the cells of mouse have integrated a candidate gene and therefore all the cells will be producing the candidate gene.” Office Action dated October 20, 2003, page 4, paragraph 3. However, as set forth below in section 3 pertaining to the declaration of Dr. Raymond Welsh, one of ordinary skill in the art would recognize the LCMV infected mouse as a model for HIV infection in human subjects, and the Specification with its working Examples is sufficiently enabling for one of ordinary skill in the art to practice the claimed invention without undue experimentation.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. See *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir.

1988). Based on the disclosure in the Specification, particularly those sections pertaining to treatment of viral disease, serpins, and serpin mimetics, one of ordinary skill in the art would be able to make and/or use the claimed invention without undue experimentation.

The Examiner has expressed concern that “the specification does not disclose as to how the level of SP16 or a serpin that is similar to a transgenic mouse can be achieved” in a subject. Office Action dated October 20, 2003, page 4, paragraph 3 through page 5, paragraph 1. This concern misses the point. As set forth above, to meet the enablement requirement, one of ordinary skill in the art must be able to make and/or use the claimed invention without undue experimentation. The declaration of Dr. Raymond Welsh, discussed in detail in section 3 below, sets forth that one of ordinary skill in the art, upon reading the Specification including the working Examples that involve use of the transgenic mouse infected with LCMV, would indeed be able to practice the claimed invention without undue experimentation. Therefore, the enablement requirement is satisfied.

It is possible that a certain amount of minimal experimentation may be required to practice the claimed invention. However, even if some experimentation may be required, it is certainly not undue experimentation. See *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976) (The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue).

3. *LCMV Infection in the Mouse is a Well-known and Established Model for Viral Infection in Humans, Including HIV Infection.*

The Examiner holds to the view that the Specification is not sufficiently enabling because it “does not teach how to induce immunity in an HIV infected subject or any subject with any disease by the claimed method.” Office Action dated March 19, 2003, page 4, paragraph 1. According to the Examiner, “it is uncertain whether there would be a therapeutic effect when the

studies obtained in a mouse model or another animals [sic] model is extended to a human subject.” Office Action dated March 19, 2003, page 6, first paragraph. The Examiner also claims that the LCMV-infected mouse disclosed in the working examples is “not a natural animal model because there is no issue of gene delivery to cells since the mouse has the transgene in all of its cells.” Office Action dated March 19, 2003, page 6, second paragraph. Further, the Examiner has argued that “a transgenic mouse infected with LCMV can not be considered [an] HIV infection animal model. Office Action dated October 20, 2003, page 5, paragraph 1. Therefore, the Examiner concludes that one of ordinary skill in the art would not be able to make and/or use the invention, particularly with regard to the treatment of viral disease such as HIV, without undue experimentation. Appellants disagree.

One of ordinary skill in the art would readily recognize that the LCMV mouse is a well-known and well-established model for HIV infection in humans, and that in view of the disclosure in the Specification, one of ordinary skill in the art would be able to make and/or use the invention without undue experimentation. In support of this position, Appellants have provided the declaration of Raymond M. Welsh, Ph.D., Professor in the Department of Pathology at the University of Massachusetts Medical Center (Worcester, MA) (Appendix C).

Dr. Welsh is a skilled virologist who understands the immunology of viral infections. Evidence of Dr. Welsh’s expertise in viral immunology is provided on page 1, paragraph 2 and page 2, paragraph 3 of Appendix C. Dr. Welsh declares that “[a] skilled virologist with an ordinary understanding of viral immunology would have recognized, at the time the above-referenced application was filed, that LCMV infection in mice is a model for determining the usefulness of the claimed invention for treating other viral diseases, including HIV.” Appendix C, page 3, paragraph 7. He also declares that “a skilled virologist with an ordinary

understanding of viral immunology would have understood, at the time the above-referenced application was filed, that LCMV infection in mice was a model for HIV infection in humans.” Appendix C, page 3, paragraph 7.

Dr. Welsh notes that his position with respect to the accepted nature of the LCMV mouse model is supported by literature that would be familiar to one having an ordinary understanding of viral immunology. Appendix C, page 3, paragraph 8. The articles cited by Dr. Welsh include Zinkernagel, *Vaccine* 20:1913-1917, 2002 (Appendix C, Exhibit 1), Klenerman and Zinkernagel, *Immunological Reviews*, 159:5-16, 1997 (Appendix C, Exhibit 2), Borrow *et al.*, *J. Virology*, 69:1059-1070, 1995 (Appendix C, Exhibit 3), Ciurea *et al.*, *Proc. Natl. Acad. Sci. USA*, 96:11964-11969, 1999 (Appendix C, Exhibit 4), and Odermatt *et al.*, *Proc. Natl. Acad. Sci. USA*, 88:8252-8256, 1991 (Appendix C, Exhibit 5). In addition, Dr. Welsh has reviewed the Specification, and has identified specific sections of the Specification that directly pertain to LCMV infection and HIV. See Appendix C, page 7, paragraph 10. Based on his review of the cited references and sections of the Specification, Dr. Welsh declares that “the present claims contain subject matter which was described in the specification in such a way as to enable a skilled virologist with an ordinary understanding of viral immunology to make and/or use the invention.”

Further, Dr. Welsh concludes that “no undue experimentation would be required for a skilled virologist with an ordinary understanding of viral immunology to make and/or use the claimed invention of the above-referenced application as it is currently claimed.” Appendix C, page 8, paragraph 12.

As discussed *supra*, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information

known in the art without undue experimentation. See *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988). Dr. Welsh's declaration clearly indicates that one of ordinary skill in the art would have understood, at the time the above-referenced application was filed, that the Specification teaches inducing or enhancing immunity in a subject against HIV, and that the claimed invention could be made and/or used without any undue experimentation.

In view of the above, Appellants have met their burden of presenting persuasive arguments, supported by suitable proof, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973). Accordingly, the rejections under 35 U.S.C. 112, first paragraph, should be overturned by the Board.

4. *The Art of Gene Therapy and Cell Therapy are not so Unpredictable as to Preclude Enablement.*

The Examiner has expressed the opinion that the Specification is not enabling because the art of gene therapy and cell therapy using CTLs is unpredictable, and the Specification does not provide any guidance as to how to address the issues of unpredictability in the art. In support of this position, the Examiner cites Romano *et al.* (Stem Cells, 18: 19-39, 2000).

The Examiner's position concerning gene therapy and cell therapy using CTLs as being inoperable is simply not the case. The abstract of Romano *et al.* states the following:

“Over the last decade, more than 300 phase I and phase II gene-based clinical trials have been conducted worldwide for the treatment of cancer and monogenic disorders. Lately, these trials have been extended to the treatment of AIDS and, to a less extent, cardiovascular diseases. There are 27 currently active gene therapy protocols for the treatment of HIV-1 infection in the USA. Preclinical studies are in progress to evaluate the possibility of increasing the number of gene therapy clinical trials for cardiomyopathies, and of beginning new gene therapy programs for neurologic illnesses, autoimmune diseases, allergies, regeneration of tissues, and to implement procedures of allogeneic tissues or cell transplantation.

In addition, gene transfer technology has allowed for the development of innovative vaccine design, known as genetic immunization. This technique has already been applied to AIDS vaccine programs in the USA. These programs aim to confer protective immunity against HIV-1 transmission to individuals who are at risk of infection.”

Romano *et al.* was published 3 years ago, and even at that time, gene therapy clinical trials were not uncommon. Romano *et al.* also indicates that gene therapy as applied to HIV disease was gaining rapid ground.

The Examiner also argues that “[w]hile the patent office has issued patents, these patents were issued for specific conditions with specific vectors and such could not be generally used in treating any condition.” Office Action dated October 20, 2003, page 5, paragraph 2. Without conceding that the claimed methods could not be applied in the treatment of other diseases or conditions, Appellants note that the claims at issue are directed to the treatment of viral disease, and not “any” disease or condition. Therefore, this line of argumentation appears misguided.

Even though gene therapy and cell therapy using CTLs may not be commonplace today from a clinical standpoint, they most certainly are sufficiently enabling for patenting. Even the PTO must admit that the number of patents that encompass these types of therapies is considerable.

While each case is taken on its own merits, the PTO cannot cling to the notion that gene therapy or CTL therapy is *per se* lacking in enablement. It is critical to make the distinction between the necessary showing under 35 U.S.C. §112, and that needed to establish clinical efficacy. Controlling precedent makes it clear that even those therapies ultimately without use in the clinic are of value, and therefore may be patented. *In re Krimmel*, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961).

Regarding the particular claims at issue, Appellants have set forth a sufficient showing to demonstrate that the disclosure is enabling for the claimed invention. Each of the arguments set forth by the Examiner has been fully addressed. Therefore, the enablement rejection under 35 U.S.C. §112, first paragraph, should be overturned by the Board. Additional reasons as to why the enablement rejection is infirmed with regard to specific claims are set forth below.

5. *The Subject Matters of Claims 42-44 and 71-73 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.*

Even if the subject matters of some of the claims is found by the Board to lack enablement, those of claims 42-44 and 71-73 do not. For this reason, these claims are separately patentable and stand or fall separately from the remaining claims.

Claims 42-44 and 71-73 contain more specific definitions of the virus to be combated. Therefore, these claims should stand or fall separately from the remaining claims in regard to the enablement rejection, which is based upon the suggestion that the specification is not enabling for the inducement of enhancement of immunity against viruses.

Unless the Examiner is able satisfy the PTO's burden of proving that these specific claims are not enabled, then this rejection should be overturned by the Board

6. *The Subject Matters of Claims 43 and 72 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.*

Claims 43 and 72 are directed towards embodiments where the virus is specifically HIV and should stand or fall separately from all the remaining claims in regard to the enablement rejection. Appellants have put forth availing arguments and evidence indicating why these claims are enabled, as discussed above. The Declaration of Dr. Welsh, among other things, establishes the enablement of these claims from the standpoint of one of skill in the art. Even, if

some of the claims directed to broader definitions of the virus to be combated were found not to be enabled by the Board, these claims are enabled.

7. *The Subject Matters of Claims 44 and 73 are Separately Patentable over those of the Remaining Claims with Regard to the Written Description Rejection.*

Claims 44 and 73 are directed specifically to LCMV and stand or fall separately from all the remaining claims in terms of the enablement rejections, based on this fact. Appellants have put forth availing arguments and evidence indicating why these claims are enabled, as discussed above. The specification contains data specifically setting forth that the methods of the invention are sufficient effect an immune response against LCMV. Therefore, even, if some of the claims directed to non-LCMV embodiments of the invention were found not to be enabled by the Board, these claims are enabled.

IX. Conclusion

In light of the foregoing, Appellants submit that the claims on appeal should not be rejected under 35 U.S.C. §112, first paragraph, on the basis of written description and enablement. Therefore, the Board is requested to overturn the rejections.

Respectfully submitted,



Mark B. Wilson
Reg. No. 37,259

FULBRIGHT & JAWORSKI, LLP
600 Congress Ave., Suite 2400
Austin TX 78701
512-536-3035 (phone)
512-536-4598 (facsimile)

APPENDIX A: PENDING CLAIMS

26. A method for enhancing or inducing immunity to a viral infection comprising expressing a serpin or a serpin mimetic in a cytotoxic T-lymphocyte of a subject by introducing an expression construct comprising a DNA segment encoding the serpin or serpin mimetic under the control of a promoter active in the cytotoxic T-lymphocyte.
27. The method of claim 26, wherein enhancing or inducing immunity comprises increasing the number of cytotoxic T-lymphocyte memory cells.
28. The method of claim 26, wherein enhancing or inducing immunity comprises augmenting cytotoxic T-lymphocyte function.
29. The method of claim 26, wherein enhancing or inducing immunity comprises augmenting cytotoxic T-lymphocyte memory cell development.
30. A method for enhancing or inducing immunity to a virus comprising:
 - a) obtaining a cytotoxic T-lymphocyte that comprises an expression vector that comprises a DNA segment encoding a serpin or a serpin mimetic under the control of a promoter active in the cytotoxic T-lymphocyte; and
 - b) administering the cytotoxic T-lymphocyte to a subject in need thereof.
31. The method of claim 30, wherein the expression vector is a viral expression construct.

32. The method of claim 31, wherein the viral expression construct is selected from the group consisting of a retrovirus, an adenovirus, an adeno-associated virus, a herpesvirus, a polyoma virus, and a vaccinia virus.
33. The method of claim 31, wherein the vector is a retroviral vector.
34. The method of claim 30, wherein the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.
35. The method of claim 30, wherein the serpin or serpin mimetic inhibits granzyme function.
37. The method of claim 30, wherein the serpin or serpin mimetic is a serpin.
38. The method of claim 30, wherein the serpin is SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, plasminogen activator inhibitor 2 (PAI-2).
39. The method of claim 38, wherein the serpin is SPI6.
40. The method of claim 38, wherein the serpin is PI9.

42. The method of claim 30, wherein the virus is HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomegalovirus, Herpes simplex 1, Herpes simplex 2, hepatitis G, enterovirus, dengue fever virus, or rabies virus.

43. The method of claim 42, wherein the virus is HIV.

44. The method of claim 42, wherein the virus is LCMV.

48. The method of claim 30, wherein inducing or enhancing immunity comprises increasing the number of cytotoxic T-lymphocyte memory cells.

49. The method of claim 30, wherein inducing or enhancing immunity comprises augmenting cytotoxic T-lymphocyte function.

50. The method of claim 30, wherein inducing or enhancing immunity comprises augmenting cytotoxic T-lymphocyte memory cell development.

61. The method of claim 26, wherein the expression construct is a viral expression construct.

62. The method of claim 61, wherein the viral expression construct is selected from the group consisting of a retrovirus, an adenovirus, an adeno-associated virus, a herpesvirus, a polyoma virus, and a vaccinia virus.

63. The method of claim 62, wherein the expression construct comprises a retroviral vector.

64. The method of claim 26, wherein the serpin or serpin mimetic inhibits granzyme activity, inhibits granzyme transcription, inhibits granzyme translation, increases granzyme degradation, or destabilizes granzyme.

65. The method of claim 26, wherein the serpin or serpin mimetic inhibits granzyme function.

66. The method of claim 26, wherein the serpin or serpin mimetic is PI9 or a PI9 mimetic.

67. The method of claim 26, wherein the serpin or serpin mimetic is a serpin.

68. The method of claim 67, wherein the serpin is SPI6, PI9, PI-6, monocyte neutrophil elastase inhibitor (MNEI), PI-8, plasminogen activator inhibitor 2 (PAI-2).

69. The method of claim 68, wherein the serpin is SPI6.

70. The method of claim 68, wherein the serpin is PI9.

71. The method of claim 26, wherein the virus is HIV, LCMV, HCV, HTLV-1, HTLV-2, EBV, HBV, human cytomegalovirus, Herpes simplex 1, Herpes simplex 2, hepatitis G, enterovirus, dengue fever virus, or rabies virus.

72. The method of claim 69, wherein the virus is HIV.
73. The method of claim 69, wherein the virus is LCMV.
74. The method of claim 30, wherein the serpin or serpin mimetic is PI9 or a PI9 mimetic.

APPENDIX B

CASES

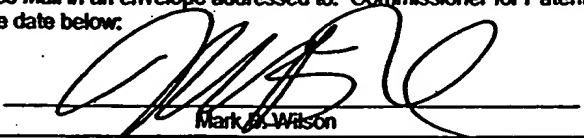
Dickinson v. Zurko, 527 U.S. 150, 158 (1999)

In re Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000)

STATUTES

35 U.S.C. §112, first paragraph

Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994

CERTIFICATE OF MAILING 37 C.F.R. §1.8	
I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231, on the date below:	
6/17/2003 Date	 Mark B. Wilson

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Philip G. ASHTON-RICKARDT and
Joseph T. OPFERMAN

Serial No.: 09/993,363

Filed: Nov. 14, 2001

For: INDUCTION OF IMMUNITY USING
INHIBITORS OF GRANZYMES

Group Art Unit: 1632

Examiner: R. R. Shukla

Atty. Dkt. No.: ARCD:382US

DECLARATION OF RAYMOND M. WELSH, PH. D., UNDER 37 C.F.R. § 1.132

Hon. Commissioner for Patents
Washington, D.C. 20231

I, Raymond M. Welsh, Ph.D., do declare that:

1. I am a United States citizen residing at 76 South Quinsigamond Ave. Unit 4, Shrewsbury, Massachusetts, 01545.
2. I currently hold the position of Professor, Department of Pathology, University of Massachusetts Medical Center (Worcester, MA). A copy of my NIH Biographical Sketch is attached as Appendix A, and a copy of my curriculum vitae is attached as Appendix B. Appendix B includes a numbered list of my publications.

3. I am a skilled virologist, who understands the immunology of viral infection, as evidenced by the following:
- I have worked with LCMV for over thirty years (since 1969), and I have collaborated and published with Nobel Lauriat Rolf Zinkernagel, whose work pertaining to LCMV is quoted and presented below.
 - I have expertise in HIV, having served on the State of California AIDS task force for about ten years.
 - I am Editor for viral immunology and pathogenesis articles for the Journal of Virology, and am in charge of the review of many of the papers on the immune response to HIV, hepatitis virus, CMV, and other viruses.
 - I study and have NIH grants on the topic of apoptosis of T cells and on T cell memory.
 - I published some of the first work on LCMV-induced T cells having enzyme-containing granules (reference #102 in Appendix B) and in documenting apoptosis as a regulator of T cell responses during LCMV infection (*e.g.*, references #121 and 135 in Appendix B).
 - In addition, I have just published a paper in the journal, *Immunity*, on T cell apoptosis in the LCMV system and in analyzing granzyme mRNA levels within these T cells.
4. I am being compensated for my time in preparing this declaration, but not for the content of my testimony.
5. I have reviewed the above-referenced application, as well as the Office Action to the above-referenced application that is dated March 19, 2003. I understand that the above-referenced application was filed on November 14, 2001.

6. I understand that the Examiner has rejected claims 26-50 of the above-referenced application because the Examiner believes that the claims contain subject matter which was not described in the specification in such a way as to enable a skilled virologist to make and/or use the invention. In addition, I understand that the Examiner believes that it would require undue experimentation for a skilled virologist to use the claimed invention as it is currently claimed. More particularly, I understand that the Examiner believes the specification does not teach inducing or enhancing immunity in a subject against human immunodeficiency virus (HIV), and that the Examiner questions whether the results disclosed in the specification, particularly those pertaining to transgenic mice and lymphocytic choriomeningitis virus (LCMV) infection, are applicable to HIV or any other virus.
7. A skilled virologist with an ordinary understanding of viral immunology would have recognized, at the time the above-referenced application was filed, that LCMV infection in mice is a model for determining the usefulness of the claimed invention for treating other viral diseases, including HIV. I believe that a skilled virologist with an ordinary understanding of viral immunology would have understood, at the time the above-referenced application was filed, that LCMV infection in mice was a model for HIV infection in humans.
8. My positions with respect to the accepted nature of the LCMV mouse model is supported by literature that would be familiar to one having an ordinary understanding of viral immunology. For example, the following papers provide facts in support of the correlation between LCMV infection and HIV infection:

Zinkernagel, Vaccine 20:1913-1917, 2002 (Exhibit 1):

On page 1914, it is noted that LCMV has contributed considerably in the past 10 years to a better understanding of HIV-AIDS pathogenesis (Table 1)." Table 1 (p. 1914) provides a summary of these contributions with references.

Klenerman and Zinkernagel, Immunological Reviews 159:5- 16, 1997 (Exhibit 2):

- Regarding the state of knowledge pertaining to LCMV infection in the mouse (page 5):

"[T]his infectious model has been established for over 60 years. The *in vivo* roles of specific immune subsets in the clearance of virus and the induction of disease are well understood. The mechanisms which allow particular virus strains to establish persistent infections have been dissected in fine detail, in particular with the use of transgenic and knockout mice."

- Regarding the rationale for comparing the LCMV mouse model to HIV (page 6):

"The reason for embarking on such a comparison is that the dominant immune response to both viruses is the cytotoxic T lymphocyte (CTL), and particular features of this immune response have striking parallels in the two infections. Since the CTL response to LCMV has been studied in immense detail, and its role *in vivo* has been accurately determined both qualitatively and quantitatively, it provides an excellent reference point from which to view the role of the same cellular response in HIV."

- An analysis of the similarities between LCMV infection and HIV infection and other viruses with regard to the role of CTL in virus infection is provided on pages 6-13.

For instance, it is noted that:

- ♦ Page 6: "The effects of CTL-mediated killing in LCMV and HIV are therefore, importantly, 2-fold: they kill infected cells and they reduce virus production."
- ♦ Page 8: "The acute response and initial control phase in both LCMV and HIV is dominated by CD8-positive MHC class I-restricted CTL."
- ♦ Page 9: "Such very high levels of CTL are by no means restricted in man to HIV, since similar responses occur in Epstein-Barr virus (EBV) during the onset of acute symptoms. Acute influenza also induces expansions of CTL with restricted TCR usage depending on HLA type of the individual, and, briefly, the capacity to kill directly *ex vivo*."

- ♦ Page 9: "Antiviral CTL remain at an elevated frequency for many months after initial LCMV infection. . . In HIV, a similar situation of active circulating CTL (Fig. 4B) and elevated precursor frequencies is seen, although, in this case, it is clear that continuous virus exposure is taking place."
- ♦ Page 10: "The loss of killing activity is central to the issue of CTL in control of viruses. The phenomenon of exhaustion was first demonstrated in LCMV, and has been proposed as a mechanism for CTL decline in HIV."
- ♦ Page 11: "The major issue in HIV is the long-term disappearance of CTL responses. . . Thus, CTL exhaustion in HIV may occur in the acute phase in an analogous manner to LCMV, or as a more chronic process in the long term. The requirements for exhaustion as defined in LCMV are extensive replication, rapid turnover of virus, infection of lymphohaemopoietic cells (plus probable extensive replication in peripheral organs) and a vigorous initial CTL response – HIV is well qualified in all these areas."
- ♦ Page 13: "Both [HIV and LCMV] induce a substantial CTL response which dominates the early stages of infection and probably determines the ultimate outcome."

Borrow et al., J. Virology, 69:1059-1070, 1995 (Exhibit 3): This paper addresses the virus-induced immunosuppression induced by LCMV, the role of virus tropism in determining pathogenicity, the role of dendritic cells. Similarities of LCMV to HIV are discussed.

- Abstract: "Our findings illustrate the key role that virus tropism may play in determining pathogenicity and, further, document a mechanism for virus-induced immunosuppression which may contribute to the clinically important immune suppression associated with many virus infections, including human immunodeficiency virus type I."
- Pages 1068-69: "Can our finding that virus infection of dendritic cells is a critical step in the production of immune suppression by LCMV clone 13 be generalized to other virus infections? It is of interest that all viruses known to be able to persist in vivo have been shown to infect cells of the immune system. . . In view of the central location of [dendritic cells] within the immune system and their unique, critical functions in the initiation of immune responses, it is likely that virus infection of dendritic cells and subsequent impairment of their functions will prove to be an underlying factor in many examples of generalized immune suppression associated with virus infection."

Ciurea et al., Proc. Natl. Acad. Sci. USA, 96:11964-11969, 1999 (Exhibit 4): This

paper discusses the persistence of LCMV at very low levels in the immune mouse, and compares the results to HIV infection and other viruses:

- Regarding similarities of LCMV to HIV and other viruses (abstract):

“The finding that LCMV-WE persists in the face of apparently intact immune responses resembles the situation in some viral (hepatitis B and C, HIV) and bacterial (tuberculosis, leprosy) infections in humans; the results are relevant to the understanding not only of other murine and human persistent viral infections but also of protective immunological memory by ‘infection immunity.’”

Odermatt et al., Proc. Natl. Acad. Sci. USA, 88:8252-8256, 1991 (Exhibit 5): This

paper shows that LCMV-induced acquired immune suppression in mice is caused by CD8⁺-T-cell-dependent elimination of macrophages/antigen-presenting cells (abstract).

- A comparison to HIV is discussed on page 8254-8255:

“A possible CD8⁺ -T-cell-dependent pathogenesis of AIDS has been proposed to explain reduction of infected or HIV-antigen-binding CD4⁺ T cells. It is conceivable that in analogy to the immunopathology observed during a LCMV infection, virus-specific cytotoxic T cells (and probably not the virus itself) may be responsible for both numerical and functional reduction of macrophages and antigen-presenting cells and thus cause destruction of follicular structures in HIV infections. Detailed histopathological studies may be taken to support the hypothesis of CD8⁺-T-cell-dependent immunopathology may significantly contribute to the pathogenesis of AIDS; lymph node histopathology in patients with AIDS-related complex is often strikingly similar to that of mice suffering from LCMV-induced immunosuppression shown here.”

9. Based on my review of these materials and my experience, a skilled virologist with an ordinary understanding of viral immunology would have understood, at the time the above-referenced application was filed, that LCMV infection in mice is a model for HIV infection in humans.

10. My review of the specification identified the following sections pertaining to LCMV infection and HIV infection:

- page 8, lines 11 –15: Indicates that the methods of the present invention provide enhanced immunity to a wide variety of viruses, including HIV and other viruses.
- page 10, lines 6-19: Indicates methods by which the present invention provides for methods for alleviating HIV infection.
- page 14, lines 6-17: Indicates that the present inventors have demonstrated the ability of granzyme B inhibitors to successfully eliminate virus, as shown using the transgenic mouse model of LCMV infection.
- page 50, line 10 through page 52, line 12; Example 1, page 67, line 22 through page 69, line 19: Provides information regarding selected experimental techniques, including production of transgenic animals, infection with LCMV, and CTL assays.
- Example 2, page 69, line 24 through page 71, line 29: Experimental results demonstrating that mouse Serpin SPI6 protects cells from apoptosis by granzyme B.
- Example 3, page 72, lines 4-31: Provides information regarding production of transgenic mice overexpressing SPI6 serpin.
- Example 4, page 74, line 5 through page 77, line 6: Results demonstrating that SPI6 protects cells from mouse granzyme B.
- Example 6, page 77, line 29 through page 78, line 10: Demonstrates that SPI6 enhances CTL activity and protects from apoptosis.
- Example 7, page 78, line 15 through page 79, line 2: Results demonstrating clonal exhaustion induced by LCMV in mice.

- Example 9, page 81, line 29 through page 83, line 4: Results demonstrating the role of SPI6 in the control of transgenic TCR CTL function.
 - Example 12, page 84, line 10 through page 88, line 25: LCMV studies demonstrating that granzyme B is involved in the development of memory cells.
11. Based on my review of these sections of the specification and in view of the literature pertaining to the usefulness of LCMV infection as a model for HIV infection, the present claims contain subject matter which was described in the specification in such a way as to enable a skilled virologist with an ordinary understanding of viral immunology to make and/or use the invention.
 12. Further, in view of the above, no undue experimentation would be required for a skilled virologist with an ordinary understanding of viral immunology to make and/or use the claimed invention of the above-referenced application as it is currently claimed.
 13. In view of the above, a skilled virologist with an ordinary understanding of viral immunology would have understood, at the time the above-referenced application was filed, that the specification teaches inducing or enhancing immunity in a subject against human immunodeficiency virus.
 14. Additionally, in view of the above, LCMV infection is a model for HIV infection that is accepted by those who work in virology and viral immunology.
 15. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of

the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

JUNE 16, 2003
Date

Raymond M. Welsh
Raymond M. Welsh, Ph.D.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. DO NOT EXCEED FOUR PAGES.

NAME Raymond M. Welsh, Ph.D.		POSITION TITLE Professor of Pathology, Molecular Genetics & Microbiology	
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
University of Massachusetts, Amherst	B.S.	1967	Microbiology
University of Massachusetts, Amherst	Ph.D.	1972	Micro/Virology
University of Kansas, Lawrence	Post-Doc	1972-1973	Micro/Biochemistry
Scripps Clinic & Research Foundation, La Jolla, CA	Post-Doc	1973-1975	Virology/Immunology

A. Positions and Honors.**Positions and Employment**

- 1972-1973 Visiting Assistant Professor of Microbiology, Univ. of Kansas, Lawrence, KS; Dept. of Microbiology
- 1975-1980 Assistant Member, Scripps Clinic and Research Foundation, La Jolla, CA; Dept. of Immunopathology
- 1979 Visiting Scientist, Karolinska Institute; Scripps Clinic, 1987.
- 1980 Adjunct Associate Professor of Pathology, Univ. California at San Diego Medical School, Dept. of Pathology,
- 1980-1985 Associate Professor of Pathology, Molecular Genetics and Microbiology, Univ. Mass. Medical School, Worcester, MA
- 1985-Present Professor of Pathology, Molecular Genetics and Microbiology, Univ. Mass. Medical School, Worcester, MA

Honors, Editorial Boards, and Advisory Groups:

Recipient of RCDA AI-00253 (1978-1983); Editorial Boards: J. Immunol. (1982-1986; 1997-present) Section Editor (2001); Proc. Soc. Exp. Biol. Med. (1978-1987); J. Virol. (1986-1989; 1991-present; Editor for Immunology and Pathogenesis 1998-present); Natural Immunity Cell Growth Regulation (1984-2000); J. Natl. Cancer Inst. (1987-1991); J. Exp. Med. (1995-present); Virology (1996-present); Study Sections: American Cancer Society (National) Immunology and Immunotherapy Section (1988-1991); American Cancer Society (Massachusetts) (1981-1991), Chairman (1985-1991); State of California AIDS Task Force (1985-1996); NIH Virology (1991-1995).

B. Selected peer-reviewed publications (of 193 publications).

- Selin, L.K., K. Vergilis, R.M. Welsh and S.R. Nahill. 1996. Reduction of otherwise remarkably stable virus-specific cytotoxic T lymphocyte (CTL) memory by heterologous viral infections. J. Exp. Med. 183:2489-2499.
- Zarozinski, C.C. and R.M. Welsh. 1997. Minimal bystander activation of CD8 T cells during the virus-induced polyclonal T cell response. J. Exp. Med. 185:1629-1639.
- Tay, C.-H. and R.M. Welsh. 1997. Distinct organ-dependent mechanisms for the control of murine cytomegalovirus infection by natural killer cells. J. Virol. 71:267-275.
- Ciupito, A.T., M. Petersson, C.L. O'Donnell, K. Williams, S. Jindal, R. Kiessling and R.M. Welsh. 1998. Immunization with an LCMV peptide mixed with heat shock protein 70 results in protective anti-viral immunity and specific CTLs. J. Exp. Med. 187:685-691.

- Szomolanyi-Tsuda, E., Q.P. Le, Garcea, and R.M. Welsh. 1998. T-independent IgG responses in vivo are elicited by live virus infection but not by immunization with viral proteins or virus-like particles. *J. Virol.* 72:6665-6670.
- Varga, S.M., and R.M. Welsh. 1998. Cutting Edge: Detection of a high frequency of virus-specific CD4⁺ T cells during acute infection with LCMV. *J. Immunol.* 161:3215-3218.
- Lin, M.Y., and R.M. Welsh. 1998. Analysis of the stability of T cell receptor (TCR) repertoire usage during lymphocytic choriomeningitis virus (LCMV) infection of mice. *J. Exp. Med.* 188:1993-2005.
- Lohman, B.L., and R.M. Welsh. 1998. Apoptotic regulation of T cells and absence of immune deficiency in virus-infected IFN- γ receptor knock-out mice. *J. Virol.* 72:7815-7821.
- Selin, L.K., S.M. Varga, I.C. Wong, and R.M. Welsh. 1998. Protective heterologous antiviral immunity and enhanced immunopathogenesis mediated by crossreactive memory T cell populations. *J. Exp. Med.* 188:1705-1715.
- Selin, L.K., M.Y. Lin, K.A. Kraemer, D.M. Pardoll, J.P. Schneck, S.M. Varga, P. Santolucito, A.K. Pinto, and R.M. Welsh. 1999. Attrition of T cell memory: selective loss of LCMV epitope-specific memory CD8 T cells following infections with heterologous viruses. *Immunity* 11:733-742.
- Welsh, R.M., T.G. Marquees, B.A. Woda, K.A. Daniels, M.A. Brehm, J.P. Mordes, D.L. Greiner, A.A. Rossini. 2000. Virus-induced abrogation of transplantation tolerance induced by donor-specific transfusion and anti-CD154 antibody. *J. Virol.* 74:2210-2218.
- Zarozinski, C.C., J.M. McNally, B.L. Lohman, K.A. Daniels, and R.M. Welsh. 2000. Bystander sensitization to activation-induced cell death as a mechanism of virus-induced immunosuppression. *J. Virol.* 74:3650-3658.
- Selin, L.K., P.A. Santolucito, A.K. Pinto, and R.M. Welsh. 2001. Innate immunity to viruses: control of vaccinia virus infection by $\gamma\delta$ T cells. *J. Immunol.* 166:6784-6794.
- Daniels, K.A., G. Devora, W.C. Lai, C.L. O'Donnell, M. Bennett, and R.M. Welsh. 2001. Murine cytomegalovirus is regulated by a discrete subset of natural killer cells reactive with monoclonal antibody to Ly49H. *J. Exp. Med.* 194:29-44.
- McNally, J.M., C.C. Zarozinski, M.Y. Lin, Brehm, M.A., Chen, H.D. and R.M. Welsh. 2001. Attrition of bystander T cells during virus-induced T cell and interferon responses. *J. Virol.* 75:5965-5976.
- Varga, S.M., Selin, L.K., and R.M. Welsh. 2001. Independent regulation of T cell memory pools: relative stability of CD4 memory under conditions of CD8 memory T cell loss. *J. Immunol.* 166:1554-1561.
- Welsh, R.M. 2001. Assessing CD8 T cell number and dysfunction in the presence of antigen. *J. Exp. Med.* 193:19-22.
- Chen, H.D., A.E. Fraire, I. Joris, M.A. Brehm, R.M. Welsh, and L.K. Selin. 2001. Memory CD8⁺ T cells in heterologous antiviral immunity and immunopathology in the lung. *Nat. Immunol.* 2:1067-1076.
- Welsh, R.M. and L.K. Selin, 2002. No one is naive: The significance of heterologous T cell immunity. *Nature Rev. Immunol.* 2:417-426.
- Brehm, M.A., A.K. Pinto, K.A. Daniels, J.P. Schneck, R.M. Welsh, L.K. Selin, 2002. T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. *Nature Immunol.* 3:627-634.
- Kim, S.-K., M.A. Brehm, R.M. Welsh, and L.K. Selin. 2002. Dynamics of memory T cell proliferation under conditions of heterologous immunity and bystander stimulation. *J. Immunol.* 169: 90-98.
- Brehm, M.A., T.G. Marquees, K.A. Daniels, D.L. Greiner, A.A. Rossini, and R.M. Welsh. 2003. Direct visualization of cross-reactive effector and memory allo-specific CD8 T cells generated in response to viral infections. *J. Immunol.* 170:4077-4086.
- Wang, X.Z., S.E. Stepp, M.A. Brehm., H.D. Chen, L.K. Selin, and R.M. Welsh. 2003. Virus-specific CD8 T cells in peripheral tissues are more resistant to apoptosis than those in lymphoid organs. *Immunity* 18:631-642.
- Zipris, D., R.M. Welsh, J.P. Mordes, J.X. Xie, D.L. Greiner, and A.A. Rossini. 2003. Infections that induce autoimmune diabetes in BBDR rats modulate CD4⁺ CD25⁺ T regulatory cell populations. *J. Immunol.* 170:3592-3602.

Principal Investigator/Program Director (Last, first, middle)
Peacock, C.D., S.-K. Kim, and
memory CD44^{hi} CD8⁺ T cells
171:0000-0000 (in press).

A. Welsh. 2003. Memory T cell attrition reduced capacity of bona-fide
respond to homeostatic and poly I:C-induced proliferation. J. Immunol.

CURRICULUM VITAE

Raymond M. Welsh, Jr.
S.S. No. 029-32-4074

Personal Data:

Date of birth: December 28, 1945
Place of birth: Montague City, Massachusetts

Education:

University of Massachusetts, Amherst, B.S., 1967 (Microbiology)
University of Miami, Coral Gables, 1967-1968 (Microbiology)
Rensselaer Polytechnic Institute, Troy, N.Y., June 1971
December 1971 (Biology/Virology)
University of Massachusetts, Amherst, Ph.D., 1972 (Microbiology/Virology)

Professional Record:

Biologist, U.S. Army Natick Laboratories, Natick, MA, Feb. 1968-Sept. 1968.
Postdoctoral Research Assoc., Dept. of Microbiology, Univ. of Kansas, Lawrence, Kansas, Feb. 1972-Aug. 1973.
Visiting Assistant Professor, Univ. of Kansas, Aug. 1972-May 1973.
Research Fellow, Dept. of Exp. Pathol., Scripps Clinic and Research Foundation, La Jolla, CA, July 1973-Dec. 1973.
Assistant Member I Dept. of Immunopathol., S.C.R.F., July 1975-June 1977.
Assistant Member II Dept. of Immunopathol., S.C.R.F., July 1977-June 1980.
Visiting Scientist, Dept. of Tumor Biology, Karolinska Institute, Stockholm, Sweden, Oct. 1979-Dec. 1979.
Adjunct Associate Professor, Dept. of Pathology, Univ. of California at San Diego, La Jolla, CA, March 1980-Sept. 1980.
Associate Professor, Dept. of Pathology and the Dept. of Molecular Genetics and Microbiology, University of Massachusetts Medical School, Worcester, MA 01605, July

1980-June 1985.

Professor, Dept. of Pathology and the Dept. of Molecular Genetics and Microbiology,
University of Massachusetts Medical School, Worcester, MA, 10605, July 1985-present.

Chairman, Interdepartmental Immunology and Virology program at UMMC (1992-
1994; 1983-84); Vice-Chairman (1990-1992);

Visiting Scientist, Scripps Clinic, La Jolla, CA, 3/87-8/87.

Research Awards:

NIH AI-17672, Immunity and Virus Disease, 1974-2004,
Principal Investigator

NIH NS-12428, Pathogenesis of MS and ALS, 1973-1980,
Co Investigator.

NIH AI-00253, Maintenance of Chronic Virus Disease,
1978-1983, Research Career Development Award.

NIH CA-34461, Regulation of Natural Killer Cells,
1983-2005, Principal Investigator

NIH AM-35506, Virus-Induced Immunopathology, 1985-2004,
Principal Investigator

NIH AI07349, Training in Immunology, 1992-2007,
Principal Investigator (Training Grant).

Professional Organizations:

American Association of Immunologists
American Society of Microbiology
Society for Experimental Biology and Medicine

Boards and Committees:

Editorial Board, Journal of Immunology, (1980-1984) (1997-Present) Proceedings of the
Society for Experimental Biology and Medicine, (1977-1988), Natural Immunity and Cell
Growth Regulation (1983-present), Journal of Virology (1986-1988; 1991-present,
Editor, 1997-present), J Natl Cancer Inst (1988-1990), Virology (1996-Present)

Arenavirus study group of the International Committee on Virus Nomenclature.

Grant Review study section of the Massachusetts Chapter of the American Cancer Society, 1981-1991; Chairman 1985-1991. Chairman of ACS Professional Scientific Advisory Committee (1994-1998)

Grant Review study section of the State of California AIDS Task Force, 1985-1996.

Grant Review National ACS study section: Immunology and Immunotherapy, 1988-1991.

NIH Virology Study Section, 1991-1995.

TEACHING EXPERIENCE

1968-69 Teaching assistant for general microbiology laboratory and for virology laboratory courses (Department of Microbiology, UMass, Amherst).

1972-73 Twice taught complete 40 lecture course in general microbiology to undergraduates (Department Microbiology, U. Kansas). Seminar course on slow virus infections (KU).

1980 Participated in laboratory course in virology for medical students at U.Cal., San Diego.

1981-present Courses at the University of Massachusetts Medical Center:

Medical student microbiology - an average of 9 lectures/year in immunology, virology, and bacteriology.

Graduate student virology - coordinator and major lecturer each year - 20 hr. lectures per year.

Graduate student advanced immunology - 3 hours of lectures/year.

BIBLIOGRAPHY

R.M. Welsh

Papers:

1. Welsh, R.M., R.S. Trowbridge, J.B. Kowalski, C.M. O'Connell and C.F. Pfau. 1971. Amantadine hydrochloride inhibition of early and late stages of lymphocytic choriomeningitis virus-cell interactions. *Virology*, 45:679-686.
2. Welsh, R.M. and C.J. Pfau. 1972. Determinants of lymphocytic choriomeningitis interference. *J. Gen. Virol.*, 14:177-187.
3. Welsh, R.M. 1972. Defective-interfering lymphocytic choriomeningitis virus. Doctoral dissertation, Univ. of Mass., Amherst.
4. Stanek, L.D., R.S. Trowbridge, R.M. Welsh, E.A. Wright and C.J. Pfau. 1972. Arenaviruses: cellular response to long-term in vitro infection with Parana and lymphocytic choriomeningitis viruses. *Infect. Immun.*, 6:444-450.
5. Pfau, C.J., R.S. Trowbridge, R.M. Welsh, L.D. Stanek and C.M. O'Connell. 1972. Arenaviruses: inhibition by amantadine hydrochloride. *J. Gen. Virol.*, 14:209-211.
6. Welsh, R.M., C.M. O'Connell and C.J. Pfau. 1972. Properties of defective lymphocytic choriomeningitis virus. *J. Gen. Virol.*, 17:355-359.
7. Pfau, C.J., R.M. Welsh and R.S. Trowbridge. 1973. Plaque assays and current concepts of regulation in arenavirus infections. In: F. Lehmann-Grube, ed., *Lymphocytic Choriomeningitis Virus and Other Arenaviruses*, Springer Verlag, New York, pp. 101-111.
8. Oldstone, M.B.A., R.M. Welsh and B.S. Joseph. 1975. Pathogenic mechanisms of tissue injury in persistent viral infections. *Ann. N.Y. Acad. Sci.*, 256:65-72.
9. Welsh, R.M., N.R. Cooper, F.C. Jensen and M.B.A. Oldstone. 1975. Human serum lyses RNA tumor viruses. *Nature*, 257:612-614.
10. Welsh, R.M., P.A. Burner, J.J. Holland, M.B.A. Oldstone, H.A. Thompson and L.P. Villarreal. 1976. A comparison of biochemical and biological properties of standard and defective lymphocytic choriomeningitis virus. *Int. Symp. on Arenaviral Infections of Public Health Importance*, Atlanta, GA, W.H.O. Bull., 52:403-408.

11. Jensen, F.C., R.M. Welsh, N.R. Cooper and M.B.A. Oldstone. 1976. Lysis of oncornaviruses by human serum. 8th Int. Cong. of Assoc. for Comparative Res. on Leukemia, Copenhagen, Oct. 1975. *Bibl. Haematol.*, 43:438-440.
12. Oldstone, M.B.A., L.H. Perrin and R.M. Welsh. 1976. Potential pathogenic mechanisms of injury in amyotrophic lateral sclerosis. In: J.M. Andrews, R.T. Johnson, M.A.B. Brazier, eds., *Amyotrophic Lateral Sclerosis: Recent Research Trends*, No. 19, Academic Press, New York, pp. 251-262.
13. Welsh, R.M., P.W. Lampert, P.A. Burner and M.B.A. Oldstone. 1976. Antibody-complement interactions with purified lymphocytic choriomeningitis virus. *Virology*, 73:59-71.
14. Welsh, R.M., F.C. Jensen, N.R. Cooper and M.B.A. Oldstone. 1976. Inactivation and lysis of oncornaviruses by human serum. *Virology*, 74:432-440.
15. Holland, J.J., L.P. Villarreal, R.M. Welsh, M.B.A. Oldstone, D. Kohne, R. Lazzarini and E. Scolnick. 1976. Long term persistent vesicular stomatitis virus and rabies virus infection of cells *in vitro*. *J. Gen. Virol.*, 33:193-211.
16. Zinkernagel, R.M. and R.M. Welsh. 1976. H-2 compatibility requirement for virus-specific T-cell mediated effector functions *in vivo*. I. Specificity of T cells conferring antiviral protection against lymphocytic choriomeningitis virus is associated with H-2K and H-2D. *J. Immunol.*, 117:1495-1520.
17. Cooper, N.R., F.C. Jensen, R.M. Welsh, Jr. and M.B.A. Oldstone. 1976. Lysis of RNA tumor viruses by human serum: Direct antibody independent triggering of the classical complement pathway. *J. Exp. Med.*, 144:970-984.
18. Welsh, R.M. Jr. 1977. Host cell modification of lymphocytic choriomeningitis virus and Newcastle disease virus altering viral inactivation by human complement. *J. Immunol.*, 118:348-354.
19. Oldstone, M.B.A., J. Holmstoen and R.M. Welsh, Jr. 1977. Alterations of acetylcholine enzymes in neuroblastoma cells persistently infected with lymphocytic chorioleningitis virus. *J. Cell. Physiol.*, 91:459-472.
20. Welsh, R.M., P.W. Lampert and M.B.A. Oldstone. 1977. Prevention of virus-induced cerebellar disease by defective-interfering lymphocytic choriomeningitis virus. *J. Infect. Dis.*, 136:391-399.
21. Merigan, T.C., M.B.A. Oldstone and R.M. Welsh. 1977. Interferon production during lymphocytic choriomeningitis virus infection of nude and normal mice. *Nature*, 268:67-68.

22. Welsh, R.M. and M.B.A. Oldstone. 1977. Inhibition of immunologic injury of cultured cells infected with lymphocytic choriomeningitis virus: Role of defective interfering virus in regulating viral antigenic expression. *J. Exp. Med.*, 145:1449-1468.
23. Welsh, R.M., Jr. and R.M. Zinkernagel. 1977. Heterospecific cytotoxic cell activity induced during the first three days of acute lymphocytic choriomeningitis virus infection in mice. *Nature*, 268:646-648.
24. Welsh, R.M., Jr. 1978. Cytotoxic cells induced during lymphocytic choriomeningitis virus infection of mice: 1. Characterization of natural killer cell induction. *J. Exp. Med.*, 148:163-181.
25. Burton, P.R., J. Steuckemann, R.M. Welsh and D. Paretsky. 1978. Some ultrastructural effects of persistent infections by the rickettsia *C. burneti* in mouse L cells and green monkey kidney (Vero) cells. *Infect. Immun.*, 21:556-566.
26. Welsh, R.M. 1978. Mouse natural killer cells: induction, specificity and function. *J. Immunol.*, 121:475-481.
27. Welsh, R.M., R.M. Zinkernagel and L.A. Hallenbeck. 1979. Cytotoxic cells induced during lymphocytic choriomeningitis virus infection of mice. II. Specificities of the natural killer cells. *J. Immunol.*, 122:475-481.
28. Welsh, R.M. and M.J. Buchmeier. 1979. Protein analysis of defective interfering lymphocytic choriomeningitis virus and persistently infected cells. *Virology*, 96:503-515.
29. Cooper, N.R. and R.M. Welsh. 1979. Antibody and complement dependent viral neutralization. *Springer Semin. Immunopathol.*, 2:285-310.
30. Welsh, R.M. and R.W. Kiessling. 1980. Natural killer cell response to lymphocytic choriomeningitis virus in beige mice. *Scand. J. Immunol.*, 11:363-367.
31. Kiessling, R. and R.M. Welsh. 1980. Killing of normal cells by activated mouse natural killer cells: evidence for two patterns of genetic regulation of lysis. *Int. J. Cancer*, 25:611-615.
32. Welsh, R.M. and L.A. Hallenbeck. 1980. Effect of virus infections on target cell susceptibility to natural killer cell-mediated lysis. *J. Immunol.*, 124:2491-2497.
33. Kiessling, R., E. Ericksson, L.A. Hallenbeck and R.M. Welsh. 1980. A comparative analysis of the cell surface properties of activated versus endogenous mouse natural killer cells. *J. Immunol.*, 125:1551-1557.

34. Welsh, R.M. and R.W. Kiessling. 1980. Activated natural killer cells induced during the lymphocytic choriomeningitis virus infection in mice. In: R. Herberman, editor, Natural Cell-Mediated Immunity Against Tumors, Academic Press, NY, pp. 671-685.
35. Welsh, R.M. and R.W. Kiessling. 1980. Modification of target sensitivity to activated mouse NK cells by interferon and virus infections. In: R. Herberman, editor, Natural Cell-Mediated Immunity Against Tumors, Academic Press, New York, pp. 963-972.
36. Hansson, M., R. Kiessling and R.M. Welsh. 1980. Interaction between NK cells and normal tissue: definition of an NK-sensitive thymocyte population. In: R. Herberman, ed., Natural Cell-Mediated Immunity Against Tumors, Academic Press, New York, pp. 855-872.
37. Buchmeier, M.J., R.M. Welsh, F.J. Dutko and M.B.A. Oldstone. 1980. The virology and immunobiology of lymphocytic choriomeningitis virus infection. Adv. Immunol., 30:275-331.
38. Zinkernagel, R.M., A. Althage, E. Waterfield, B. Kindred, R. Welsh, G. Callahan and P. Pincetl. 1980. Restriction specificities, alloreactivity and allotolerance expressed by T cells from nude mice reconstituted with H-2 compatible thymus grafts. J. Exp. Med., 151:376-399.
39. Zinkernagel, R.M., R.M. Welsh, G. Callahan and A. Althage. 1980. On the immunocompetence of H-2 incompatible irradiation bone marrow chimeras. J. Immunol., 124:2356-2365.
40. Altman, A., J.M. Cardenas, R.M. Welsh, Jr. and D.H. Katz. 1980. The biological effects of allogeneic effect factor on T lymphocytes. III. Interferon does not contribute to the biological activities displayed by AEF on both T and B lymphocytes. Ann. Inst. Pasteur Immunol., 131C:335-347.
41. Welsh, R.M. and M.V. Haspel. 1977. Meeting Report. Membrane viruses and immune responses. Clin. Immunol. Immunopathol. 8:150-155.
42. Hansson, M., R. Kiessling, B. Andersson and R.M. Welsh. 1980. Effect of interferon and interferon inducers on the NK sensitivity of normal mouse thymocytes. J. Immunol., 125:2225-2231.
43. Welsh, R.M. and W.F. Doe. 1980. Cytotoxic cells induced during lymphocytic choriomeningitis virus infection of mice. III. Natural killer cell activity in cultured spleen leukocytes concomitant with T cell dependent immune interferon production. Infect. Immun., 30:473-483.

44. Welsh, R.M. 1981. Natural killer cells in virus infections. *Curr. Top. Microbiol. Immunol.*, 92:83-106.
45. Welsh, R.M., Karre, M. Hansson, L.A. Kunkel and R.W. Kiessling. 1981. Interferon-mediated protection of normal and tumor target cells against lysis by mouse natural killer cells. *J. Immunol.*, 126:219-225.
46. Kunkel, L.A. and R.M. Welsh. 1981. Metabolic inhibitors render "resistant" target cells sensitive to natural killer cell mediated lysis. *Int. J. Cancer*, 27:73-79.
47. Welsh, R.M. 1981. Do natural killer cells play a role in virus infections? *Antiviral Res.*, 1:5-12.
48. Yogeewaran, G., A. Gronberg, M. Hansson, T. Dalianis, R. Kiessling and R.M. Welsh. 1981. Correlation of glycosphingolipids and sialic acid in YAC-1 lymphoma variants with their sensitivity to natural killer cell mediated lysis. *Int. J. Cancer*, 28:517-526.
49. Biron, C.A. and R.M. Welsh. 1982. Activation and role of natural killer cells in virus infections. *Med. Microbiol. Immunol.*, 170:155-172.
50. Yogeewaran, G., R. Fujinami, R. Kiessling and R.M. Welsh. 1982. Interferon induced alterations in cellular sialic acid and glycoconjugates. Correlation with susceptibility to activated natural killer cells. *Virology*, 121:363-371.
51. Yogeewaran, G., R.M. Welsh, A. Gronberg, R. Kiessling, M. Patarrayo, G. Klein, M. Gidlund, H. Wigzell and K. Nilsson. 1982. Surface sialic acid of tumor cells inversely correlated with susceptibility to natural killer cell mediated lysis. *In*: R.B. Herberman, ed., *NK Cells and Other Natural Effector Cells*, Vol. 2. Academic Press, New York, pp. 765-770.
52. Biron, C.A. and R.M. Welsh. 1982. Proliferation and role of natural killer cells during viral infection. *In*: R.B. Herberman, ed., *NK Cells and Other Natural Effector Cells*, Academic Press, New York, pp. 493-498.
53. Welsh, R.M., C.A. Biron, J.F. Bukowski, S. Habu, M.V. Haspel, K. Holmes, K. Okumura and D.C. Parker. 1983. Regulation and role of natural cell-mediated immunity during virus infections. *In*: F.A. Ennis, ed., *Human Immunity to Viruses*, Academic Press, New York, pp. 21-41.
54. Welsh, R.M. 1984. Natural killer cells and interferon. *CRC Crit. Rev. Immunol.*, 5:55-93.

55. Yogeeswaran, G., A. Gronberg, R.M. Welsh and R.W. Kiessling. 1983. Interferon-induced increase in neuraminidase releasable sialic acid and glycosphingolipid metabolism in mouse lymphoma and L1210 leukemic cell lines: correlation with susceptibility to natural killer cell mediated lysis. *Int. J. Cancer*, 31:501-508.
56. Biron, C.A. and R.M. Welsh. 1982. Blastogenesis of natural killer cells during viral infection in vivo. *J. Immunol.*, 129:2788-2795.
57. Bukowski, J.F., C.A. Biron and R.M. Welsh. 1983. Elevated natural killer cell-mediated cytotoxicity, plasma interferon and tumor cell rejection in mice persistently infected with lymphocytic choriomeningitis virus. *J. Immunol.*, 131:991-996.
58. Biron, C.A., G. Sonnenfeld and R.M. Welsh. 1984. Interferon induces natural killer cell blastogenesis in vivo. *J. Leukocyte Biol.*, 35:31-37.
59. Biron, C.A., L.R. Turgiss and R.M. Welsh. 1983. Increase in NK cell number and turnover rate during acute virus infection. *J. Immunol.*, 131:1539-1545.
60. Bukowski, J.F., B.A. Woda, S. Habu, K. Okumura and R.M. Welsh. 1983. Natural killer cell depletion enhances virus synthesis and virus induced hepatitis in vivo. *J. Immunol.*, 131:1531-1538.
61. Welsh, R.M., C.A. Biron and J.F. Bukowski. 1984. The interplay between NK cells and virus infections. D. Schlessinger, ed., *Microbiology-1984*, American Society of Microbiology, Washington, D.C. pp. 320-323.
62. McIntyre, K.W., J.F. Bukowski and R.M. Welsh. 1985. Exquisite specificity of adoptive immunization in arenavirus-infected mice. *Antiviral Res.*, 5:299-305.
63. Woda, B.A., M.L. McFadden, R.M. Welsh and K.M. Bain. 1984. Separation and isolation of rat natural killer (NK) cells from T cells with monoclonal antibodies. *J. Immunol.*, 132:2183-2184.
64. Biron, C.A., S. Habu, K. Okumura and R.M. Welsh. 1984. Lysis of uninfected and virus infected cells in vivo: a rejection mechanism in addition to that mediated by natural killer cells. *J. Virol.*, 50:698-707.
65. Bukowski, J.F., B.A. Woda and R.M. Welsh. 1984. Pathogenesis of murine cytomegalovirus infection in natural killer cell depleted mice. *J. Virol.*, 52:119-128.
66. Bukowski, J.F. and R.M. Welsh. 1985. Interferon enhances the susceptibility of virus-infected fibroblasts to cytotoxic T cells. *J. Exp. Med.*, 161:257-262.
67. Bukowski, J.F., J.R. Warner, G. Dennert and R.M. Welsh. 1985. Adoptive transfer studies demonstrating the antiviral effect of natural killer cells in vivo. *J. Exp. Med.*,

68. Yang, H., G. Yogeewaran, J.F. Bukowski and R.M. Welsh. 1985. Expression of asialo GM₁ and other antigens and glycolipids on natural killer cells and spleen leukocytes in virus-infected mice. *Nat. Immun. Cell Growth Regul.*, 4:21-39.
69. Welsh, R.M., J.F. Bukowski and C.A. Biron. 1985. Regulation of virus infections by natural killer cells. *Fed. Proc.* (In Press).
70. Welsh, R.M., C.A. Biron, J.F. Bukowski, K.W. McIntyre and H. Yang. 1984. Role of natural killer cells in virus infections of mice. *Surv. Synth. Pathol. Res.*, 3:409-431.
71. Bukowski, J.F. and R.M. Welsh. 1985. Inability of interferon to protect virus-infected cells against lysis by natural killer (NK) cells correlates with NK cell-mediated antiviral effects in vivo. *J. Immunol.*, 135:3537-3541.
72. Yang, H., I. Joris, G. Majno and R.M. Welsh. 1985. Necrosis of adipose tissue induced by sequential infections with unrelated viruses. *Am. J. Pathol.*, 120:173-177.
73. Holmes, K.V., R.M. Welsh and M.V. Haspel. 1986. Natural cytotoxicity against mouse hepatitis virus-infected target cells. I. Correlation of cytotoxicity with virus binding to leukocytes. *J. Immunol.*, 136:1446-1453.
74. Welsh, R.M., M.V. Haspel, D.C. Parker and K.V. Holmes. 1986. Natural cytotoxicity against mouse hepatitis virus infected cells. II. A cytotoxic cell with a B lymphocyte phenotype. *J. Immunol.*, 136:1454-1460.
75. Yang, H. and R.M. Welsh. 1986. Induction of alloreactive cytotoxic T lymphocytes by acute virus infection of mice. *J. Immunol.*, 136:1186-1193.
76. Biron, C.A., R.J. Natuk and R.M. Welsh. 1986. Generation of large granular T lymphocytes in vivo during viral infection. *J. Immunol.*, 136:2280-2286.
77. Welsh, R.M., C.A. Biron, J.F. Bukowski, K.W. McIntyre, R.J. Natuk and H. Yang. 1986. Regulation of viral infections by large granular lymphocytes. In: *Leukocytes and Host Defense*, Alan R. Liss, Inc., NY pp. 403-410.
78. Biron, C.A., K.F. Pedersen and R.M. Welsh. 1986. Purification and target cell range of in vivo-elicited blast natural killer cells. *J. Immunol.*, 137:463-471.

79. Biron, C.A. and R.M. Welsh. 1986. Antigenic distinctions and morphological similarities between proliferating NK and cytotoxic T cells. In: E. Lotzova and R.B. Herberman, eds., *Natural Immunity, Cancer and Biological Response Modification*. S. Karger AG, Basel pp. 289-297.
80. Bukowski, J.F. and R.M. Welsh. 1986. The role of natural killer cells and interferon in resistance to acute infection of mice with herpes simplex virus type 1. *J. Immunol.*, 136:3481-3485.
81. Welsh, R.M. 1986. Regulation of virus infections by natural killer cells. *Nat. Immun. Cell Growth Regul.*, 5:169-199.
82. Welsh, R.M. 1986. Regulation of virus infections by cytotoxic leukocytes. *Clin. Immunol. Newsletter*, 7:171-175.
83. Yang, H. and R.M. Welsh. 1986. Induction of allospecific and virus-specific memory cytotoxic T cells during arenavirus infections. *Med. Microbiol. Immunol.*, 175:137-139.
84. Welsh, R.M. 1987. Regulation and role of large granular lymphocytes in arenavirus infections. *Curr. Top. Microbiol. Immunol.*, 134:185-209.
85. Bukowski, J.F. and R.M. Welsh. 1986. Enhanced susceptibility to cytotoxic T lymphocytes of target cells isolated from virus-infected or interferon-treated mice. *J. Virol.*, 59:735-739.
86. Bukowski, J.F. and R.M. Welsh. 1986. Virus-induced interferon modulates susceptibility of tissue to attack by T cells and NK cells. In, *Interferons as Cell Growth Inhibitors and Antitumor Factors*, Alan R. Liss, Inc., N.Y. pp. 175-184.
87. Natuk, R.J., K.W. McIntyre and R.M. Welsh. 1987. Infiltration and chemotaxis of natural killer/large granular lymphocytes during virus infection. *Prog. Leukocyte Biol.*, 6:41-50.
88. Natuk, R.J. and R.M. Welsh. 1987. Accumulation and chemotaxis of natural killer/large granular lymphocytes to sites of virus replication. *J. Immunol.*, 138:877-883.
89. McIntyre, K.W. and R.M. Welsh. 1986. Accumulation of natural killer and cytotoxic T large granular lymphocytes in the liver during virus infection. *J. Exp. Med.*, 164:1667-1681.
90. Biron, C.A., K.F. Pedersen and R.M. Welsh. 1987. Aberrant T cells in beige mutant mice. *J. Immunol.*, 138:2050-2056.

91. McIntyre, K.W., R.J. Natuk, C.A. Biron, K. Kase, J. Greenberger and R.M. Welsh. 1988. Blastogenesis and proliferation of large granular lymphocytes in non-lymphoid organs. *J. Leukocyte Biol.*, 43:492-501.
92. Natuk, R.J. and R.M. Welsh. 1987. Chemotactic effect of human recombinant interleukin-2 on mouse activated large granular lymphocytes. *J. Immunol.*, 139:2737-2743.
93. Bukowski, J.F., K.W. McIntyre, H. Yang and R.M. Welsh. 1987. Natural killer cells are not required for interferon-mediated prophylaxis against vaccinia or murine cytomegalovirus infections. *J. Gen. Virol.*, 68:2219-2222.
94. Welsh, R.M., H. Yang and J.F. Bukowski. 1988. The role of interferon in the regulation of virus infections by cytotoxic lymphocytes. *Bioessays*, 8:10-13.
95. Welsh, R.M., R.J. Natuk, K.W. McIntyre, H. Yang, C.A. Biron and J.F. Bukowski. 1988. Factors influencing the control of virus infections by natural killer cells. In: C. Reynolds and R. Wiltout, eds., *Functions of the Natural Immune System*, Plenum Publishing Corp., N.Y. pp. 111-128.
96. Welsh, R.M., H. Yang and K.W. McIntyre. 1988. Function of natural killer cells in lymphocytic choriomeningitis infection. In: C. Lopez, ed., *Immunobiology and Pathogenesis of Persistent Virus Infections*. American Society of Microbiology, Washington, D.C. pp. 125-134.
97. Yang, H. and R.M. Welsh. 1988. Induction of allospecific cytotoxic T cells by virus infections in vivo. In: P. Ivanyi, ed., *MHC + X. Complex Formation and Antibody Induction*, Springer-Verlag, Berlin, pp. 1-6.
98. Bukowski, J.F., H. Yang and R.M. Welsh. 1988. The antiviral effect of lymphokine-activated killer (LAK) cells. 1. Characterization of the effector cells mediating prophylaxis. *J. Virol.*, 62:3642-3648.
99. Natuk, R.J., J.F. Bukowski and R.M. Welsh. 1989. Antiviral effect of lymphokine-activated killer (LAK) cells. 2. Chemotaxis and homing to sites of infection. *J. Virol.*, 63:4969-4971.
100. Yang, H., P.L. Dundon, S.R. Nahill and R.M. Welsh. 1989. Virus-induced polyclonal cytotoxic T lymphocyte stimulation. *J. Immunol.*, 142:1710-1718.
101. Welsh, R.M., P.L. Dundon, E.E. Eynon, J.O. Brubaker, G.C. Koo and C.L. O'Donnell. 1990. Demonstration of the antiviral role of natural killer cells in vivo with a natural killer cell-specific monoclonal antibody (NK 1.1). *Nat. Immun. Cell Growth Regul.*, 9:112-120.

102. Welsh, R.M., W.K. Nishioka, R. Antia and P.L. Dundon. 1990. Mechanism of killing by virus-induced cytotoxic T cells elicited in vivo. *J. Virol.*, 64:3726-3733.
103. Welsh, R.M. 1990. Methods for studying mouse natural killer cells. In: M.B.A. Oldstone, ed., *Viral Pathogenesis: A Practical Approach*. IRL Press Ltd., Oxford, England, pp. 121-135.
104. Welsh, R.M. and H.R. Robinson. 1993. Infection of immune cells by viruses. In: I.V. Roitt and P.J. Delves, eds., *Encyclopedia of Immunology*, Academic Press Ltd., London, Vol 3, 1560-1562.
105. Brubaker, J.O., K.T. Chong and R.M. Welsh. 1991. Lymphokine-activated killer (LAK) cells are rejected in vivo by activated natural killer cells. *J. Immunol.*, 147:1439-1444.
106. Welsh, R.M., J.O. Brubaker, M. Vargas-Cortes, and C.L. O'Donnell. 1991. Natural killer (NK) cell response to virus infections in mice with severe combined immunodeficiency. The stimulation of NK cells and the NK cell-dependent control of virus infections occur independently of T and B cell function. *J. Exp. Med.*, 173:1053-1063.
107. Welsh, R.M. and M. Vargas-Cortes. 1992. Regulation and role of natural killer cells in virus infections. In: C.B. Lewis and J.O'D.M. Gee, eds., *The Natural Immune System. The Natural Killer Cell*. IRL Press, Oxford, pp 107-150.
108. Welsh, R.M. and H.I. McFarland. 1993. Mechanisms of viral pathogenesis. In: N.S. Young, ed., *Viruses and Bone Marrow*, Marcel Dekker, New York, pp. 3-30.
109. Nishioka, W.K. and R.M. Welsh. 1992. Inhibition of cytotoxic T lymphocyte-induced target cell DNA fragmentation, but not lysis, by inhibitors of DNA topoisomerases I and II. *J. Exp. Med.* 175:23-27.
110. Guberski, D.L., V.A. Thomas, W.R. Shek, A.A. Like, E.S. Handler, A.A. Rossini, J.E. Wallace and R.M. Welsh. 1991. Induction of Type I diabetes by Kilham's rat virus in diabetes-resistant BB/Wor rats. *Science* 254:1010-1013.
111. Vargas-Cortes, M., C.L. O'Donnell, M.C. Appel, K.S. Yurkunis and R.M. Welsh. 1992. A lymphocyte differentiation and activation antigen, CZ-1, that distinguishes between CD8⁺ and unstimulated CD4⁺ T lymphocytes. *Eur. J. Immunol.* 22:1043-1047.
112. Welsh, R.M. 1993. Lymphocytic choriomeningitis virus-general features. In: R.G. Webster and A. Granoff, eds., *Encyclopedia of Virology*. W.B. Saunders Co., Orlando, FL, pp. 801-811.

113. Vargas-Cortes, M., C.L. O'Donnell, J.W. Maciaszek and R.M. Welsh. 1992. Generation of "NK-escape" variants of Pichinde virus during acute and persistent infections. *J. Virol.* 66:2532-2535.
114. Welsh, R.M., P.R. Rogers and R.R. Brutkiewicz. 1993. Class I MHC antigens and the control of virus infections by NK cells. In, M.V. Sitkovsky and P. Henkart, Eds., *Cytotoxic Cells: recognition, effector functions, generation, and methods*, Birkhauser (Springer/Verlag), Boston, pp. 400-406.
115. McFarland, H.L., S.R. Nahill, J.W. Maciaszek and R.M. Welsh. 1992. CD11b (Mac-1): A marker for CD8⁺ cytotoxic T cell activation and memory in virus infection. *J. Immunol.* 149:1326-1333.
116. Brutkiewicz, R.R., S.J. Klaus and R.M. Welsh. 1992. Window of vulnerability of vaccinia virus-infected cells to natural killer cell-mediated cytotoxicity correlates with enhanced NK cell triggering and is concomitant with a decrease in H-2 Class I antigen expression. *Natural Immun.* 11:203-214.
117. Nahill, S.R., and R.M. Welsh. 1992. Polyclonality of the cytotoxic T lymphocyte response to virus infection. *Proc. Soc. Exp. Biol. Med.* 200:453-457.
118. Nishioka, W.K., and R.M. Welsh. 1993. B cells induce apoptosis via a novel mechanism in fibroblasts infected with mouse hepatitis virus. *Natural Immun.* 12:113-127.
119. Brutkiewicz, R.R., C.L. O'Donnell, J.W. Maciaszek, R.M. Welsh, and M. Vargas-Cortes. 1993. The mAb CZ-1 identifies a mouse CD45-associated epitope expressed on IL-2-responsive cells. *Eur. J. Immunol.* 23:2427-2433.
120. Nahill, S.R., and R.M. Welsh. 1993. High frequency of cross-reactive cytotoxic T lymphocytes elicited during the virus-induced polyclonal CTL response. *J. Exp. Med.* 177:317-327.
121. Razvi, E.S., and R.M. Welsh. 1993. Programmed cell death of T lymphocytes during acute viral infection: a mechanism for virus-induced immune deficiency. *J. Virol.* 67:5754-5765.
122. Brown, D.W., R.M. Welsh, and A.A. Like. 1993. Infection of peripancreatic lymph nodes but not islets precedes Kilham rat virus-induced diabetes in BB/Wor rats. *J. Virol.* 67:5873-5878.
123. Kurilla, M.G., S. Swaminathan, R.M. Welsh, E. Kieff, and R.R. Brutkiewicz. 1993. Effects of virally expressed interleukin-10 on vaccinia virus infection in mice. *J. Virol.* 67:7623-7628.

124. Selin, L.K., S.R. Nahill, and R.M. Welsh. 1994. Cytotoxic T cell cross-reactivity between heterologous viruses during acute viral infections. *J. Exp. Med.* 179:1933-1943.
125. Szomolanyi-Tsuda, E., P.L. Dundon, I. Joris, L.D. Shultz, B.A. Woda, and R.M. Welsh. 1994. Acute, lethal NK cell-resistant myeloproliferative disease induced by polyomavirus in SCID mice. *Am. J. Pathol.* 144:359-371.
126. Nishioka, W.K., and R.M. Welsh. 1994. Susceptibility to CTL-induced apoptosis is a function of the proliferative status of the target. *J. Exp. Med.* 179:769-774.
127. Welsh, R.M., C.L. O'Donnell, and L.D. Shultz. 1994. Antiviral activity of NK1.1⁺ natural killer cells in C57BL/6 SCID mice infected with murine cytomegalovirus. *Natural Immun.* 13:239-245.
128. Moore, T.A., M. Vargas-Cortes, R.M. Welsh, M. Bennett, and V. Kumar. 1994. Expression of CZ-1: a CD45RB epitope on progenitors of natural killer and other hematopoietic cells. *Scand. J. Immunol.* 39:257-266.
129. Selin, L.K., and R.M. Welsh. 1994. Specificity and editing by apoptosis of virus-induced CTL. *Curr. Opinion Immunol.* 6:553-559.
130. Tay, C.-H., R.M. Welsh, and R. R. Brutkiewicz. 1995. Natural killer cell response to viral infections in β_2 -microglobulin deficient mice. *J. Immunol.* 154:780-789.
131. Welsh, R.M., L.K. Selin, and E.S. Razvi. 1995. Role of apoptosis in the regulation of virus-induced T cell responses, immune suppression, and memory. *J. Cell. Biochem.* 59:135-142.
132. Brutkiewicz, R.R., and R.M. Welsh. 1995. Major histocompatibility complex Class I antigens and the control of viral infections by natural killer cells. *J. Virol.* 69:3967-3971.
133. Razvi, E., R.M. Welsh, and H.L. McFarland. 1995. The in vivo state of antiviral cytotoxic T lymphocyte precursors: characterization of a cycling cell population containing CTLp in immune mice. *J. Immunol.* 154:620-632.
134. Zarozinski, C.C., E.F. Fynan, L.K. Selin, H.L. Robinson and R.M. Welsh. 1995. Protective CTL-dependent immunity and enhanced immunopathology in mice immunized by particle bombardment with DNA encoding an internal virion protein. *J. Immunol.* 154:4010-4017.
135. Razvi, E.S., Z. Jiang, B.A. Woda and R.M. Welsh. 1995. Lymphocyte apoptosis during the silencing of the immune response to acute viral infections in normal, *lpr*, and Bcl-2-transgenic mice. *Am. J. Pathol.* 147:79-91.
136. Varga, S.M. and R.M. Welsh. 1996. The CD45RB-associated epitope defined by

- monoclonal antibody CZ-1 is an activation and memory marker for mouse CD4 T cells. *Cell. Immunol.* 167:56-62.
137. Selin, L.K., K. Vergilis, R.M. Welsh and S.R. Nahill. 1996. Reduction of otherwise remarkably stable virus-specific cytotoxic T lymphocyte (CTL) memory by heterologous viral infections. *J. Exp. Med.* 183:2489-2500.
 138. Szomolanyi-Tsuda, E. and R.M. Welsh. 1996. T cell-independent antibody-mediated clearance of polyoma virus in T cell-deficient mice. *J. Exp. Med.* 183:403-411.
 139. Welsh, R.M. and G.C. Sen. 1996. Non-specific host responses to viral infections. In: N. Nathanson, ed., *Viral Pathogenesis*. Lippincott-Raven Publishers, NY., pp. 109-142.
 140. Welsh, R.M., C.-H. Tay, S.M. Varga, C.L. O'Donnell, K.L. Vergilis, and L.K. Selin. 1996. Lymphocyte-dependent 'natural' immunity to virus infections mediated by both natural killer and memory T cells. *Seminars in Virology*. 7:95-102.
 141. Zarozinski, C.C., and R.M. Welsh. 1997. Minimal bystander activation of CD8 T cells during the virus-induced polyclonal T cell response. *J. Exp. Med.* 185:1629-1639.
 142. Lohman, B.L., E.S. Razvi and R.M. Welsh. 1996. T lymphocyte down regulation following acute viral infection is not dependent on CD95 (Fas) receptor/ligand interactions. *J. Virol.* 70:8199-8203.
 143. Tay, C.-H., and R.M. Welsh. 1997. Distinct organ-dependent mechanisms for the control of murine cytomegalovirus infection by natural killer cells. *J. Virol.* 71:267-275.
 144. Selin, L.K., and R.M. Welsh. 1997. Cytolytically active memory CTL present in lymphocytic choriomeningitis virus (LCMV)-immune mice after clearance of virus infection. *J. Immunol.* 158:5366-5373.
 145. Welsh, R.M., and R.T. Woodland. 1998. "Viruses, infection of immune cells by." In: *Encyclopedia of Immunology*, Academic Press Ltd. pp 2484-2487.
 146. Karre, K., and R.M. Welsh. 1997. Viral decoy vetoes killer cell. *Nature* 386:446-447.
 147. Ciupitu, A.-M.T., M. Petersson, C.L. O'Donnell, K. Williams, S. Jindal, R. Kiessling, and R.M. Welsh. 1998. Immunization with a lymphocytic choriomeningitis virus peptide mixed with heat shock protein 70 results in protective antiviral immunity and specific cytotoxic T lymphocytes. *J. Exp. Med.* 187:685-691.
 148. Welsh, R.M., M.-Y. Lin, B.L. Lohman, S.M. Varga, C.C. Zarozinski, and L.K. Selin. 1997. $\alpha\beta$ and $\gamma\delta$ T-cell networks and their roles in natural resistance to viral

infections. *Immunol. Rev.* 159:79-93.

149. Tay, C.-H., E. Szomolanyi-Tsuda and R.M. Welsh. 1998. Control of infections by NK cells. *Curr. Topics Microbiol. Immunol.* 230:193-220.
150. Selin, L.K., S.M. Varga, I.C. Wong, and R.M. Welsh. 1998. Protective heterologous antiviral immunity and enhanced immunopathogenesis mediated by crossreactive memory T cell populations. *J. Exp. Med.* 188:1105-1715
151. Varga, S.M., and R.M. Welsh. 1998. Stability of virus-specific CD4+ T cell frequencies from acute infection into long term memory. *J. Immunol.* 161:367-374.
152. Welsh, R.M., C.L. O'Donnell, D.J. Reed, and R.P. Rother. 1998. Evaluation of the GAL α 1-3 GAL epitope as a host modification factor eliciting natural humoral immunity to enveloped viruses. *J. Virol.* 72:4650-4656.
153. Lohman, B.L., and R.M. Welsh. 1998. Apoptotic regulation of T cells and absence of immune deficiency in virus-infected IFN- γ receptor knock-out mice. *J. Virol.* 72:7815-7821.
154. Lin, M.Y., and R.M. Welsh. 1998. Stability and Diversity of T cell receptor (TCR) repertoire usage during lymphocytic choriomeningitis virus (LCMV) infection of mice. *J. Exp. Med.* 188:1993-2005
155. Szomolanyi-Tsuda, E., and R.M. Welsh. 1998. T cell-independent anti-viral antibody responses. *Curr. Opin. Immunol.* 10:431-435.
156. Szomolanyi-Tsuda, E., Q.P. Le, R. L. Garcea, and R.M. Welsh. 1998. T cell-independent IgG responses in vivo are elicited by live virus infection, but not by immunization with viral proteins or virus-like particles. *J. Virol.* 72:6665-6670.
157. Varga, S.M., and R.M. Welsh. 1998. Cutting Edge: Detection of a high frequency of virus-specific CD4+ T cells during acute infection with LCMV. *J. Immunol.* 161:3215-3218.
158. Welsh, R.M. Lymphocytic choriomeningitis virus as a model for the study of cellular immunology. 1999. In, M. W. Cunningham and R. J. Fujinami, eds, *Effects of microbes on the immune system*. Lippincott, Williams and Wilkins, Philadelphia, pp. 280-312.
159. Selin, L.K., M.Y. Lin, S.M. Varga, and R.M. Welsh. 1999. CD8 memory to viruses and the T cell network. In: M.V. Sitkovsky and P.A. Henkart, Eds, *Cytotoxic cells: Basic mechanisms and medical applications*. Lippincott, Williams and Wilkins, Philadelphia, pp. 327-362.
160. Tay, C.-H., L.Y.Y. Yu, V. Kumar, L. Mason, J.R. Ortaldo, and R.M. Welsh. 1999. The role of LY49 NK cell subsets in the regulation of murine cytomegalovirus infections. *J.*

161. Welsh, R.M., and J.M. McNally. 1999. Immune deficiency, immune silencing, and clonal exhaustion of T cell responses during viral infections. *Curr. Opin. Microbiol.* 2:382.
162. Selin, L.K., M.Y. Lin, K.A. Kraemer, D.M. Pardoll, J.P. Schneck, S.M. Varga, P. Santolucito, A.K. Pinto, and R.M. Welsh. 1999. Attrition of T cell memory: selective loss of LCMV epitope-specific memory CD8 T cells following infections with heterologous viruses. *Immunity* 11:733-742.
163. Welsh, R.M., T.G. Markees, B.A. Woda, K.A. Daniels, M.A. Brehm, J.P. Mordes, D.L. Greiner, A.A. Rossini. 2000. Virus-induced abrogation of transplantation tolerance induced by donor-specific transfusion and anti-CD154 antibody. *J. Virol.* 74:2210-2218.
164. Peacock, C.D., M.Y. Lin, J.R. Ortaldo, and R.M. Welsh. 2000. The virus-specific and allospecific CTL response to lymphocytic choriomeningitis virus is modified in a subpopulation of CD8⁺ T cells co-expressing the inhibitory major histocompatibility complex class I receptor Ly49G2. *J. Virol.* 74:7032-7038.
165. Zarozinski, C.C., J.M. McNally, B.L. Lohman, K.A. Daniels, and R.M. Welsh. 2000. Bystander sensitization to activation-induced cell death as a mechanism of virus-induced immune suppression. *J. Virol.* 74:3650-3658.
166. Szomolanyi-Tsuda, E., J.D. Brien, J.E. Dorgan, R.M. Welsh, and R.L. Garcea. 2000. The role of CD40-CD154 interaction in antiviral T cell-independent IgG responses. *J. Immunol.* 164:5877-5882.
167. Selin, L.K., P.A. Santolucito, A.K. Pinto, and R.M. Welsh. 2001. Innate immunity to viruses: control of vaccinia virus infection by $\gamma\delta$ T cells. *J. Immunol.* 166:6784-6794.
168. Varga, S.M., and R.M. Welsh. 2000. High frequency of virus-specific interleukin-2-producing CD4⁺ T cells and Th1 dominance during lymphocytic choriomeningitis virus infection. *J. Virol.* 74:4429-4432.
169. Lin, M.Y., L.K. Selin, and R.M. Welsh. 2000. Evolution of the CD8 T cell repertoire during infections. *Microbes and Infection* 2:1025-1039.
170. Welsh, R.M., J.M. McNally, M.A. Brehm, and L.K. Selin. 2000. Consequences of crossreactive and bystander CTL responses during viral infections. *Virology* 270:4-8.
171. McNally, J.M., C.C. Zarozinski, M.Y. Lin, and R.M. Welsh. 2001. Attrition of bystander T cells during virus-induced T cell and interferon responses. *J. Virol.* 75:5965-5976.
172. Szomolanyi-Tsuda, E., J.D. Brien, J.E. Dorgan, R.L. Garcea, R.T. Woodland, and R.M. Welsh. 2001. Antiviral T cell-independent type 2 antibody responses induced in vivo

in the absence of T and NK cells. *Virology*. 280:160-168.

173. Turgeon, N.A., N.N. Iwakoski, N.E. Phillips, W.C. Meyers, R.M. Welsh, D.L. Greiner, J.P. Mordes, and A.A. Rossini. 2000. Viral infection abrogates CD8⁺ T cell deletion induced by costimulation blockade. *J. Surg. Res.* 93:63-69.
174. Kiessling, R., G. Pawelec, R.M. Welsh, J.D. Barry, and S. Ferrone. 2000. Have tumor cells learnt from microorganisms how to fool the immune system? *Molecular Medicine Today* 6:344-346.
175. Varga, S.M., L.K. Selin and R.M. Welsh. 2001. Independent regulation of T cell memory pools: relative stability of CD4 memory under conditions of CD8 memory T cell loss. *J. Immunol.* 166:1554-1561.
176. Szomolanyi-Tsuda, E., M.S. Brehm, and R.M. Welsh. 2002. Acquired immunity against virus infections. In: S.H.E. Kaufman, A. Sher and R. Ahmed, Eds. *The anti-infective immune response*. American Society of Microbiology Press, Washington, D.C., p. 247-265.
177. McNally, J.M. and R.M. Welsh. 2002. Bystander T cell activation and attrition. *Curr. Top. Microbiol. Immunol.* 263:29-41.
178. Welsh, R.M. 2001. Assessing CD8 T cell number and dysfunction in the presence of antigen. *J. Exp. Med.* 193:F19-22.
179. Daniels, K.A., G. Devora, W.C. Lai, C.L. O'Donnell, M. Bennett, and R.M. Welsh. 2001. Murine cytomegalovirus is regulated by a discrete subset of natural killer cells reactive with monoclonal antibody to Ly49H. *J. Exp. Med.* 194:29-44.
180. Varga, S.M., X. Wang, R.M. Welsh and T.J. Braciale. 2001. Immunopathology in RSV infection is mediated by a discrete oligoclonal subset of antigen-specific CD4⁺ T cells. *Immunity* 15:637-646.
181. Welsh, R.M. 2001. Brief encounter. *Nature* 411:541-542.
182. Chen, H.D., A.E. Fraire, I. Joris, M.A. Brehm, R.M. Welsh, and L.K. Selin. 2001. Memory CD8⁺ T cells in heterologous antiviral immunity and immunopathology in the lung. *Nat. Immunol.* 2:1067-1076.
183. Welsh, R.M., S.E. Stepp, E. Szomolanyi-Tsuda, C.D. Peacock, 2002. Tumor viral escape from inhibited T cells. *Nat Immunol.* 3:112-114.
184. Forman D., R.M. Welsh, T.G. Markes, B.A. Woda, J.P. Mordes, A.A. Rossini, 2002. Viral abrogation of stem cell transplantation tolerance causes graft rejection and host death by different mechanisms. *J Immunol.* 168:6047-6056.
185. Brehm, M.A., A.K. Pinto, K.A. Daniels, J.P. Schneck, R.M. Welsh, L.K. Selin,

2002. T cell immunodominance and maintenance of memory regulated by unexpectedly cross-reactive pathogens. *Nat. Immunol.* 3:627-634
186. Welsh, R.M. and L.K. Selin, 2002. No one is naive: The significance of heterologous T cell immunity. *Nat. Rev. Immunol.* 2:417-426.
187. Kim, S.-K., M.A. Brehm, R.M. Welsh, and L.K. Selin. 2002. Dynamics of memory T cell proliferation under conditions of heterologous immunity and bystander stimulation. *J. Immunol.* 169:90-98.
188. Brehm, M.A., T.G. Markees, K.A. Daniels, D.L. Greiner, A.A. Rossini, and R.M. Welsh. 2003. Direct visualization of cross-reactive effector and memory allo-specific CD8 T cells generated in response to viral infections. *J. Immunol.* 170:4077-4086.
189. Wang, X.Z., S.E. Stepp, M.A. Brehm., H.D. Chen, L.K. Selin, and R.M. Welsh. 2003. Virus-specific CD8 T cells in peripheral tissues are more resistant to apoptosis than those in lymphoid organs. *Immunity* 18:631-642.
190. Peacock, C.D., S.-K. Kim, and R. M. Welsh. Memory T cell attrition: reduced capacity of bona-fide memory CD44^{hi} CD8⁺ T cells to respond to homeostatic and poly I:C-induced proliferation. *J. Immunol.* 171:0000-0000 (in press) .
191. Zipris, D., R.M. Welsh, J.P. Mordes, J.X. Xie, D.L. Greiner, and A.A. Rossini. Infections that induce autoimmune diabetes in BBDR rats modulate CD4⁺ CD25⁺ T regulatory cell populations. *J. Immunol.* 170:3592-3602.
192. Peacock, C.D., W. Xu, S.E. Stepp, and R.M. Welsh. 2002. Dynamics of LY49 expressing cytotoxic lymphocyte subsets in response to infection. *Microbes and Infection* 4:1481-1490.
193. Welsh, Raymond M., Stepp, Susan E., Szomolanyi-Tsuda, Eva. 2003. B cell memory: Sapping the T cell. *Nature Medicine*. Vol.9, 2:164-166.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☒ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.